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HUNGER OEDEMA¹

By F A DENZ

Introduction

HUNGER oedema is a condition endemic in many Eastern countries where large populations exist on the edge of starvation. However, it is only during war or famine when millions are affected, or when oedema appears in a people usually free from this disorder, that it excites interest and investigation. Historical accounts have been given by Maver (1920) and Lusk (1921), who showed that it is a condition long recognized as the lot of the citizens of beleaguered cities, and of prisoners, both civil and military. Great attention was given to hunger oedema by German observers in 1917 and 1918 after the widespread appearance of oedema in German civilians. At this time many detailed clinical accounts were published (Falta, 1917, Falta and Quittner, 1917, Knack and Neumann, 1917, Rubner, 1918, Rössle, 1919). Throughout the recent war of 1939-45, reports indicate a widespread incidence—in the Dutch East Indies (Streef, G M, Streef-Spaan, A M, and Ismail, 1940), India (Chakrabarty, 1944), the Hadramaut (Ankalkar, 1944), the Japanese-occupied area of China (Laycock, 1944), and the German-occupied territories of France (Gounelle, Marche, and Bachet, 1942, Leulier, Revol, and Trouillas, 1942, Beaussart, Feullet, and Secques, 1943), Belgium (Govaerts and Lequime, 1942, Brull and Dumont, 1942), and Greece (Perakis and Bakalos, 1943). Hunger oedema has also been reported amongst German civilians (Landes, 1943) and in German prison camps (Stevenson, 1944, Mollison, 1946).

Though many theories have been advanced to explain hunger oedema, it is now widely accepted that the main factor is a deficiency of dietary protein, which in turn results in a depleted protein-content of the body and particularly of the blood-plasma. Starling (1895) suggested the importance of the colloid osmotic pressure in fluid exchanges in the body, from which developed the view that the plasma-protein molecules, by virtue of their size, are unable to diffuse to any appreciable extent across the capillary wall, and hence that the plasma-proteins exert an osmotic pressure which prevents an excessive accumulation of fluid in the tissues. A decrease in plasma-proteins, which commonly occurs in hunger oedema, results in a fall of the plasma osmotic pressure, a diminished ability to hold fluid in the capillaries, and a consequent diffusion into and collection in the tissues of an excess of fluid. Support for this hypothesis has been provided by the results of the experimental lowering of plasma-proteins in animals by plasmapheresis (Barker

¹ Received July 16, 1946

and Kirk, 1930, Darrow, Hopper, and Cary, 1932; Leiter, 1931) and by protein-deficient diets (Frisch, Mendel, and Peters, 1929, Weech, Goettsch, and Reeves, 1934) A lowered plasma-protein content has been the common finding in hunger oedema in man and has been reported by Jansen (1918), Mahwa (1917), Schittenhelm and Schlecht (1918), Weech and Ling (1931), Gounelle, Marche, and Bachet (1942), Govaerts and Lequime (1942), Mollison (1946), and others

In the present investigation the plasma-protein levels in a small number of cases of oedema occurring amongst German civilian internees have been

TABLE I

Total Plasma-protein (gm per 100 c c)

Normal British	Internees, no history of oedema	Internees, after bed rest at camp	Slight oedema (±)	Moderate oedema (+)	Severe oedema (++)
6.46	5.79	6.46	4.77	6.14	5.10
7.40	6.08	6.14	4.10	4.02	5.79
6.82	5.44	5.98	5.78	4.62	4.02
6.82	5.78	6.30	5.78	4.62	4.10
7.12	5.10	5.78	5.10	4.77	4.77
6.46	6.46	6.14	—	5.09	4.95
7.82	6.14	6.14	—	6.14	4.55
7.82	6.46	5.98	—	4.44	—
7.49	6.46	5.44	—	—	—
6.46	6.46	5.78	—	—	—
6.46	6.46	6.14	—	—	—
—	6.46	6.46	—	—	—
—	6.14	—	—	—	—
—	6.14	—	—	—	—

Arithmetic mean

7.04	6.16	6.03	5.11	5.07	4.84
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Standard deviation

0.53	0.47	0.27	0.64	0.64	0.51
------	------	------	------	------	------

Coefficient of variation per cent

7.5	7.4	4.4	12.3	12.7	10.5
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investigated The copper-sulphate method of Phillips, Van Slyke, Dole, Emerson, Hamilton, and Archibald (1945) was used to determine the total plasma-proteins The values for oedematous and non-oedematous cases are given in Table I Oedema was classified as slight (±) when confined to the feet, moderate (+) when well developed in feet and ankles, and severe (++) when it spread to the legs and in a few cases to the abdomen and face Gross oedema was not found in any of these cases

Table I shows that the internees had a plasma-protein level significantly lower than that of a control group of British soldiers Further, the degree of oedema appeared to be proportional to the lowering of the plasma-protein, but there is considerable variation in each group The normal limits for total plasma-protein are given by Moore and Van Slyke (1930) as 6.2 to 8.0 gm per 100 c c by micro-kjeldahl methods The 'critical' level of protein

below which hunger oedema occurs is claimed to be 5 gm per 100 c c (Weech and Ling, 1931). A similar 'critical' level has been reported in nephrosis (Moore and Van Slyke, 1930, Muntweyler, Way, Binns, and Myers, 1933, Peters, 1932, and Peters, Wakeman, Eisenman, and Lee, 1929), while in animals the 'critical' level of plasma-proteins for oedema in protein starvation is said to be higher than in protein deficiency resulting from plasmapheresis (Weech, Snelling, and Goettsch, 1933). These authors also observed that retention of fluid begins with the first diminution of plasma-protein and progresses steadily as the total proteins continue to fall. It seems that the 'critical' level of total plasma-proteins is the value below which accumulation of fluid is invariably evident, as pitting oedema of the dependent parts of the body. That oedema may occur at higher plasma-protein concentrations in malnutrition than in plasmapheresis experiments arises, it is thought, because the circulation in malnutrition is less efficient or because the loss of fat has diminished the elasticity of the subcutaneous tissues (Peters, 1935). From Table I it will be seen that in the present series most of the oedema cases had plasma-protein values below 5 gm per 100 c c. Clinically recognizable oedema was found in some cases where the plasma-protein was above 6 gm per 100 c c, and thus well above the reported 'critical' level. These findings suggest that a fixed 'critical' level does not exist. It seems more probable that oedema commences with the first lowering of the plasma-proteins and that it becomes apparent relatively soon in some of the poorly covered subjects of malnutrition in the easily distensible subcutaneous tissues of the legs.

Plasma-albumen Levels

Plasma-albumen, having a much smaller molecule than globulin, is the predominant protein in the production of the colloid osmotic pressure of the plasma. Thus Govaerts (1927) stated that the osmotic pressure of one gram of albumen is equivalent to 7.50 cm of water, as contrasted with 1.95 cm for one gram of globulin. Weech and Ling (1931) emphasized that albumen deficiency is the real cause of nutritional oedema, and found in oedematous Chinese patients that when the albumen exceeds 2.9 gm per 100 c c oedema is not observed, but when it is less than 2.5 gm oedema is invariably present. Martin and Demole (1942), reviewing recent French papers on hunger oedema, stated that in moderate oedema the albumen range is 4.0 to 4.5 and in severe oedema 2.5 to 3.0 gm per 100 c c.

In the present series of cases the plasma-proteins were fractionated, and the fibrinogen, albumen, and globulin estimated by the modification of Hawk and Bergeim's method described by Beaumont and Dodds (1943). The results are given in Table II.

The normal range for plasma-albumen is given by Moore and Van Slyke (1930) as 3.6 to 5.0 gm per 100 c c, and Trevorrow, Kaser, Patterson, and Hill (1941) gave the mean value for normal adults as 4.70 ± 0.32 gm per

100 c.c. From Table II it will be seen that most of the values for plasma-albumen are low, but the degree of oedema bears no relation to the plasma-albumen. The concept of a critical level of plasma-protein for the production of oedema has been criticized above, and the same arguments prevail against a 'critical' albumen level. The accuracy of the clinical assessment of oedema is discussed more fully below. The most that can be said is that oedema in these cases is associated with low plasma-albumen levels in accordance with

TABLE II

Plasma-protein Fractions in Oedema (gm per 100 c.c.)

Total protein	Fibrinogen	Globulin	Albumen	Degree of oedema
4.00	0.23	1.19	2.58	±
4.50	0.35	1.41	2.75	++
4.28	0.24	1.26	2.78	++
4.70	0.38	1.48	2.84	+
4.88	0.21	1.69	2.96	±
4.70	0.24	1.40	3.00	++
5.55	0.28	2.10	3.08	±
4.67	0.27	1.11	3.29	±
4.43	0.21	0.88	3.34	+
5.26	0.39	1.54	3.46	±
5.47	0.37	1.60	3.48	++
5.26	0.25	1.44	3.57	+
5.07	0.23	1.26	3.58	+
4.81	0.17	0.83	3.81	+

the theory of oedema production derived from Starling's views on fluid exchanges.

The plasma-globulin in these cases is variable, as found by other investigators and summarized by Drinker and Yoffey (1941). Low values for plasma-albumen tend to be associated with a similar lowering for globulin, but this association is very inconstant.

Plasma-volume

A low blood-volume has been reported in cases of hunger oedema by Lusk (1921). These values probably reflect the general loss of tissue as a result of malnutrition. Mollison (1946) found in seriously under-nourished subjects that the blood-volume is not reduced in proportion to body weight. He found low ratios of blood-volume to body weight in three oedematous cases, but other similar cases did not show this relation. A lowered blood-volume might be anticipated because of loss of fluid into tissues with resultant haemoconcentration, but Lusk (1921) has reported hydraemia, as have German workers of the 1917-18 period. This would indicate that the blood shares the excessive hydration of the body, and the hydraemia might be expected to result in a raised blood-volume.

Plasma-volumes in the cases under investigation were determined by the Evans blue (T 1842) method. Ten milligrams of Evans blue in 5 c.c. of sterile water was injected intravenously and blood samples were taken at 5, 10, 15, 20, 30, and 60 minutes. From the curve of the plasma concentrations

obtained colorimetrically, a line was drawn asymptotic and extrapolated to give the concentration at zero time. Values given in Table III were obtained.

The results given in Table III show considerable variation. Plasma-volumes per square metre of body surface probably form the best basis for comparison, and Rowntree and Brown (1929) give the normal range for male adults as 1.40 to 2.5 litres (average 1.94) per square metre. The results in

TABLE III
Plasma-volumes in Oedema

Plasma-protein (gm per 100 c.c.)	Oedema	Plasma-volume (litres)	Haema-tocrit %	Blood-volume (litres)	Plasma-volume (litres per kilo)	Plasma-volume (litres per sq metre)	Day of test
5.26	+	3.90	39	6.39	0.060	2.05	4 days after admission
4.28	++	3.00	34	4.54	0.052	1.79	3 " " "
4.43	+	2.95	39	4.41	0.054	1.76	3 " " "
4.70	++	3.14	36	4.91	0.048	1.74	Day of admission
5.55	++	2.80	36	4.40	0.054	1.75	" " "
4.67	±+	2.90	35	4.46	0.055	1.79	" " "
5.07	+	3.75	42	6.47	0.058	2.08	" " "
5.47	++	4.50	37	7.16	0.075	2.60	" " "
4.88	±	5.00	39	8.20	0.075	2.63	" " "
5.39	±	5.15	32	7.58	0.086	3.14	" " "
4.50	++	5.35	35	8.28	0.099	3.30	" " "

TABLE IV
Variations of Plasma-volumes (litres)

Plasma-protein (gm per 100 c.c.)			Haemoglobin (%)			Plasma-volume (litres per sq metre)		
1st day	5th day	Increase	1st day	5th day	Increase	1st day	5th day	Decrease
4.95	5.78	0.83	11.9	14.0	2.1	3.34	2.21	1.13
5.78	6.32	0.54	10.7	13.4	2.7	3.14	2.36	0.78
5.44	5.78	0.34	12.5	13.6	1.1	2.60	2.15	0.45

Table III show values as high as 3.30 litres per square metre. Consideration of these somewhat unexpected findings disclosed that normal values were obtained when the examination was done several days after admission to hospital, whereas high values were frequently obtained when the plasma-volume was determined within a few hours of admission. This suggested a change in plasma-volume within a few days of admission to hospital. To investigate this point the plasma-volumes, total plasma-proteins, and haemoglobin of three oedematous patients were determined on admission and again after five days' rest in bed in hospital. The results are given in Table IV.

Table IV shows that in a period of five days all three cases gained in plasma-protein and haemoglobin, at the same time showing marked decrease in plasma-volume as measured by the Evans blue method. In five days the plasma-protein increased from 6 to 17 per cent and haemoglobin from 9 to

25 per cent This is in excess of any gain that might be expected in five days from improved diet A similar rise in protein from 4.5 to 5.7 gm per 100 c.c. on loss of oedema has been recorded by Gounelle, Bachet, and Marche (1943) It appears likely that the blood of these patients was hydraemic on admission and that loss of the extra water from the blood resulted in an increase in both plasma-proteins and haemoglobin The apparent fall in plasma-volume cannot be entirely accounted for by the disappearance of excess fluid from the circulation In all three cases the decrease was far in excess of that which could be computed from the figures for plasma-protein and haemoglobin In one case the increase in plasma-protein and haemoglobin was 17 per cent, while the plasma-volume decreased by 34 per cent Only part of the fall in apparent plasma-volume can be attributed to loss of water from the blood-stream, and a further explanation must be sought

The use of Evans blue for the determination of plasma-volumes is justified only as long as it can be shown to be confined to the circulatory system Evans blue is believed to be firmly adsorbed on the plasma-proteins (Courtice, 1943) and hence is confined to the same circulation area as the plasma-proteins, but it has been clearly shown that oedema fluids may have considerable protein content which is apparently attained by exudation from the capillaries into the tissue spaces The protein content of oedema fluid produced by a variety of causes ranges from mere traces up to 4 gm per 100 c.c. Nutritional oedema fluid usually shows values of less than 0.5 gm per 100 c.c. (Weech, Goettsch, and Reeves, 1934, Bramkamp, 1935, Weech, Snelling, and Goettsch, 1933), but even at this concentration a volume of oedema fluid of 7 to 10 litres would contain a very large amount of protein capable of retaining Evans blue That Evans blue is not confined to the blood-stream has been shown by Calvin (1941) in states of asphyxia, and Freeman, Freedman, and Miller (1941) in shock, while Hevesy, Köster, Sørensen, Warburg, and Zerah (1943) have detected it in bile, and Ferrebee, Leigh, and Berliner (1941) have found it in the thoracic lymph of dogs Courtice (1943), however, has shown in dogs and goats that only about 0.5 per cent of the injected dye appears in the thoracic lymph in one hour

It is evident that Evans blue can leak into the subcutaneous tissue, and the high values for plasma-volumes given above are due partly to the hydraemic condition and partly to the leakage of the dye, although in most cases the amount of dye diffusing from the vessels in the course of the experiment is probably small The Evans blue thus distributes itself to the blood-plasma, the oedema-fluid, and the lymph It is impossible to evaluate the proportion of the observed volume due to each of these fluid systems It has been suggested that this difficulty of diffusion of the dye can be overcome by extrapolating the series of readings to zero time before leakage has occurred (Gibson and Evans, 1937, Gregersen and Stewart, 1939) Gilder, Muller, and Phillips (1940) have shown that mixing in the blood-stream is probably complete within five minutes They showed also that the concentration falls at a moderate rate for a still longer period prior to flattening out to the

constant elimination curve Extrapolation of this so-called 'mixing curve' gave a smaller plasma-volume than that estimated by extrapolation of the elimination curve and probably more nearly represents the true plasma-volume

From the results in Tables III and IV it can be concluded that the high values for plasma-volume in oedema cases are in part the result of raised plasma-volume due to hydraemia A further factor affecting these results is a loss of dye by diffusion from the vascular system The use of the method of extrapolation of the elimination curve has not entirely overcome the difficulty of diffusion of Evans blue It is probable that diffusion of the dye commences immediately it has been injected, but the rate of diffusion is unlikely to be high enough to invalidate the method

The Effect of Rest on Oedema

Reference has already been made to increase in plasma-proteins and other changes found in oedema cases within a few days of admission to hospital These rapid changes, which are a most striking feature of hunger oedema, may be summarized

- 1 Loss of oedema in two to four days
- 2 Loss of weight in the same period, three to seven kilos in weight is lost in a few days
- 3 Passage of large volumes of urine in the first 48 hours, as much as 10 litres of urine may be passed in this time
- 4 Loss of chloride in the urine is considerable, 45 gm. of chloride may be passed in 48 hours
- 5 Fall in plasma-chloride level
- 6 Decrease in plasma-volume as measured by the Evans blue method
- 7 A slight initial fall in plasma-protein followed an irregular but definite rise over the following five days

Several factors may be concerned in the production of these changes The internee had exchanged an inactive life in an internment camp on a diet of 2,000 calories with about 20 gm of protein for a bed in a British Hospital and a diet of from 3,000 to 3,500 calories with from 70 to 100 gm of protein The simplest explanation of the physiological changes described above would be that the increased protein of the diet raised the plasma-protein with resultant increase in plasma osmotic pressure and withdrawal of fluid from the oedematous tissue to the blood-stream Against this explanation is the fact that the oedema disappeared in a few days, long before the plasma-protein deficiency could be made good by diet Further, it can be shown that these changes may be the result of rest in the absence of any improvement in diet In the internment camp oedema is successfully resolved by rest in bed without change in diet The fact that rest was a simple means of resolving oedema was appreciated by the German writers of the war of 1914-18 (Schittenhelm and Schlecht, 1918, Knack and Neumann, 1917), who realized also that the

oedema recurred on return to an active life. German writers of that period have pointed out that exercise is a potent factor in the production of oedema (Falta, 1917, Jurgens, 1916). The same story has been told of oedema in Allied prisoners of the war of 1939-45. The prisoners had no oedema while living in prison camps, but rapidly developed oedema when forced to make long marches across Germany.

Effect of Exercise on Oedema

In the present investigation the effect of exercise was examined. Four patients whose oedema had disappeared within five days of admission to

TABLE V

Effect of Exercise on Oedema in Four Cases

	On admission	After five days in bed	After seven days' exercise	After eight days in bed
Weight	54	51.5	53	52
Plasma proteins	4.95	5.78	5.44	5.98
Plasma-volume	3.30	2.21	2.60	1.99
Weight	60	58	58	58
Plasma-proteins	5.44	5.78	6.14	6.14
Plasma-volume	2.60	2.15	1.82	1.92
Weight	60	52.5	53	53
Plasma-proteins	5.78	6.31	6.48	6.14
Plasma-volume	3.14	2.36	1.38	2.32
Weight	55	52.25	53	53
Plasma-proteins	5.10	4.96	5.28	5.62

Weight in kilos

Plasma-proteins in gm. per 100 c.c.

Plasma volumes in litres per sq. metre of body surface

hospital were taken as a group. Their régime was changed from passive lying in bed to an active, ambulant life. They rose at 6 a.m. and sat or walked about until 8 p.m. with only one hour of rest in bed at midday. In addition they had two periods of active exercise which consisted of walking for a period of two to three hours daily. The diet continued unchanged at over 3,000 calories.

Within six days all four cases showed slight but definite pitting oedema of the feet, and three showed slight gains in weight. The plasma-proteins remained high during this period, and indeed in two cases showed a protein level consistently above 6 gm. per 100 c.c. The changes are shown in Table V.

From Table V it will be seen that the first patient gained 1.5 kilos in weight, while developing oedema and showing evidence of hydration of the blood as indicated by a slight fall in plasma-protein. The increased plasma-volume can also be interpreted as due to an increased extracellular fluid content. The other three cases did not show any significant changes, other than the development of oedema and in two cases a slight gain in weight. After seven days of exercise these patients were returned to bed for a period

of eight days. Within the first two days of this second period of rest the oedema disappeared. In three cases the plasma-proteins fell during the first day of rest (thirteenth day after admission to hospital) and this fall might be attributed to the deviation of fluid from the tissues to the blood prior to elimination by the kidneys. Thereafter the plasma-proteins rose slightly. These changes in plasma-protein, shown in Figs 1 and 2, are discussed in greater detail below.

As a complementary experiment to the production of oedema by exercise in apparently cured cases, an attempt was made to maintain oedema by

TABLE VI

Effect of Exercise plus Good Diet on Oedema in Two Cases

	On admission	After seven days' exercise	After eight days in bed
Weight	63.5	63.5	59.5
Plasma-proteins	5.10	5.10	5.10
Plasma-volume	2.70	2.63	1.86
Weight	76.25	76	75
Plasma proteins	4.77	5.28	5.97
Plasma-volume	1.75	2.16	2.03
Weight in kilos			
Plasma-proteins in gm per 100 c c			
Plasma-volumes in litres per sq. metre of body surface			

exercise in spite of increased diet. Two cases of oedema, one of moderate degree and one of minor degree, immediately on admission to hospital were submitted to the active régime described above. They were at the same time given the full diet of 3,000 calories. After seven days they had preserved their oedema unchanged, their weight was constant, and plasma-proteins and plasma-volumes had not shown significant changes. They were then treated by rest in bed. The oedema disappeared in two days and there was significant loss of weight. The changes are given in Table VI.

These experiments show that exercise results in the persistence of oedema and that rest in bed is a simple means of resolving oedema. This change, however, is reversible and the oedema readily and rapidly recurs if exercise is resumed, as has been shown here and reported elsewhere (Knack and Neumann, 1917, Schittenhelm and Schlecht, 1918, Govaerts and Lequime, 1942, Stevenson, 1944).

Permanent cure can be obtained only by replacing the protein deficiencies of the body, as has been shown experimentally in man by Gounelle, Bachet, and Marche (1943). The peculiar changes on rest and exercise remain an interesting but subsidiary part of the problem of oedema.

Plasma-proteins in Oedema

The plasma-protein values for the oedema cases studied above after loss of oedema show values not far removed from 6 gm per 100 c c. The plasma-proteins of another series of treated oedema cases have been determined and

are shown in Column 3 of Table I. These cases were treated in the internment camp by rest in bed without any increase in diet. Under these conditions they soon lost their oedema. The plasma-proteins of 12 such cases after loss of oedema gave a mean value of 6.03 gm. per 100 c.c. The transitory nature of the cure by rest is shown by the fact that many of these patients redeveloped oedema within a short time of resuming normal camp life. The reversible change from oedema to the non-oedematous state is due in the internment camp entirely to exercise and posture, since the diet remains the same through-

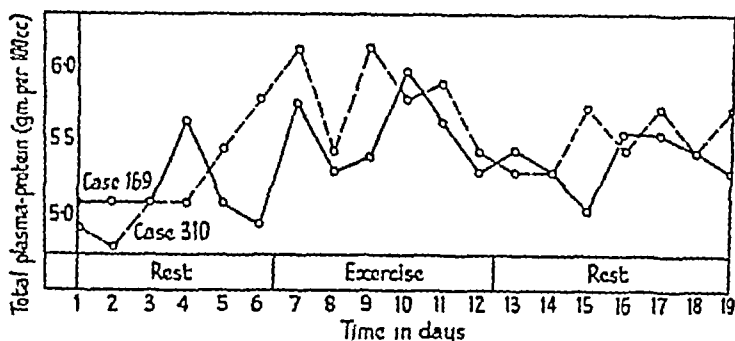


FIG 1 Daily variation in plasma-protein

out. At first sight it is somewhat surprising that oedema so readily appears in a group whose proteins are approximately 6 gm. per 100 c.c., but consideration of the various factors shows that the plasma-protein is but one of the factors concerned and gives a very incomplete and sometimes inaccurate picture of the nutritional state of the body. Burch and Winsor (1944) have emphasized the importance of the elasticity of the skin in restraining oedema formation. Even a slight lowering of plasma-proteins may result in defective absorption of fluid that can readily collect under the influence of gravity in the lax and inelastic tissues of the victim of under-nutrition.

If the plasma-protein figures for cases of oedema after resolution of oedema by rest (Column 3, Table I) are compared with the values for internees who have no history of oedema (Column 2, Table I), it is evident that there is no significant difference between the plasma-proteins for the two groups, although both are lower than normal controls (Column 1, Table I). From these figures the conclusion that large numbers of internees are on the verge of oedema is probably justified. Indeed, this conclusion is supported by the occurrence of minor epidemics of oedema whenever internees are moved from one camp to another or are for any other reason assuming a more active role.

The constancy of the plasma-protein in the normal subject is usually accepted without question. When daily plasma-protein determinations are made on oedema cases, some show considerable fluctuation. Thus, Case 169 in Fig 1 shows diurnal variations of sufficient magnitude to obscure changes produced by diet or exercise and certainly to render insignificant random determinations of plasma-proteins. Yet another case, 762 in Fig 2, shows

consistent regularity except for a fall in plasma-protein on the second and thirteenth days that can be accounted for by a transitory hydraemia arising from a change of regime from exercise to rest. Even these changes are significant from the point of view of the commonly accepted idea of the constancy of the plasma-protein.

This diurnal variation resulted in a consideration of the accuracy of methods for determination of proteins. The values obtained by the copper-sulphate method of Phillips, Van Slyke, Dole, Emerson, Hamilton, and Archibald (1945),

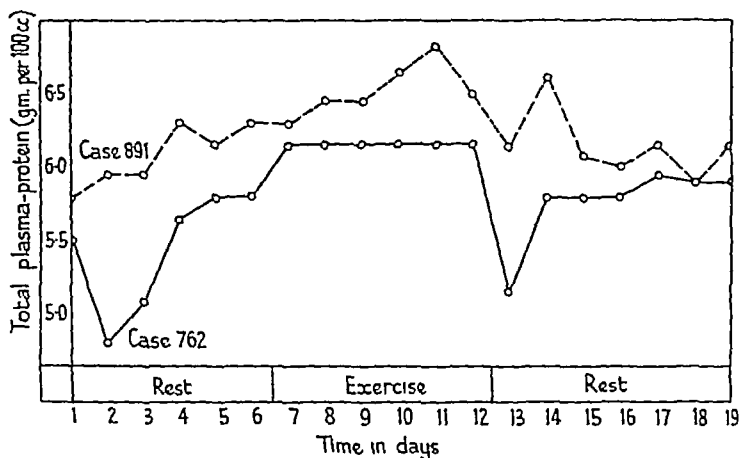


FIG 2 Daily variation in plasma-protein

used throughout the present investigation, were compared with values obtained by digestion-Nesslerization methods and very close agreement was obtained. Errors resulting mainly from faulty methods of collection of blood have been investigated by Rowe (1916), Peters, Wakeman, and Eisenman (1926), and Kagan (1941). Consideration of the possible errors did not disclose any likely factor to account for the magnitude of variations obtained, and the regularity of the values for Case 762 suggests that the variations in Case 169 are not due to errors in technique, since these two cases were examined together by the same methods. Ingestion of water and of saline has been shown in normal young adults to produce considerable change in plasma-protein, by Lyons, Jacobson, and Neerkin (1945), who attributed such changes to variations in serum-protein, and quoted the conclusions of Madden and Whipple (1940) that the serum-proteins are in a state of dynamic equilibrium and are added to or taken from the blood with ease. It seems improbable that the malnourished oedema cases should show much variation in total amount of protein owing to depleted protein reserves. The changes appear rather to be due to the labile nature of water exchanges in the body in oedema cases, with the production of varying degrees of hydraemia. This variation appears to be an individual characteristic and not directly related to the degree of oedema or the plasma-protein content. It is apparent at least in hunger oedema that

the plasma-protein is not a fixed quantity, and several factors may be concerned in the diurnal changes found in some oedema cases

Extracellular Fluid and Oedema

That the degree of clinical oedema does not bear a constant relation to the plasma-protein level can be seen from Tables I and II. One patient showed only slight oedema of the ankles, but lost in a few days $8\frac{1}{2}$ kilos in weight and excreted 28 gm of chloride in two days. Within one week he had lost about $8\frac{1}{2}$ litres of oedema fluid. Another case showed gross oedema up to the knees. In a week he lost only two kilos in weight, corresponding to two litres of oedema fluid. The degree of oedema as shown by the subcutaneous collection of fluid apparently gives no certain measure of the degree of hydration of the body.

The location of the oedema is of interest. If a body contains $8\frac{1}{2}$ litres of excess fluid and yet shows minimal visible oedema which could at the most account for one litre, the fluid must be hidden in the body. It is unlikely that hydraemia could result in the accommodation of more than half a litre in the blood-stream. This leaves unaccounted seven litres. Some light was thrown on this problem at post-mortem of two internees (not included in the present series) who died of natural causes. Both bodies were somewhat emaciated, but showed no clinical oedema on external examination. Internal examination, however, showed occult oedema. The meninges and brain were oedematous. The mediastinal tissues were distended with fluid to a gelatinous consistency, and the perirenal and retroperitoneal tissues had a similar appearance. The association of emaciation with gelatinous oedema of the deep connective tissue gives an indication of the occult nature of oedema and the location of large amounts of oedema fluid.

From these findings it is evident that clinically assessed oedema gives an inaccurate picture of the fluid-content of the body. The changes in weight during the loss of oedema have provided the most useful indication of the degree of oedema. An attempt was made to determine the amount of oedema by following the changes in the extracellular fluid volume as determined by the thiocyanate method. It has been inferred that the distribution of thiocyanate in the body corresponds roughly to the extracellular fluid (Lands, Cutting, and Larson, 1940, Mellors, Muntwyler, and Mautz, 1941, Wallace and Brodie, 1939, Weir and Hastings, 1939).

The procedure adopted was to inject intravenously 5 cc of a 5-molar solution of ammonium thiocyanate sterilized by Seitz filtration. A fresh syringe was used, the needle being already in the vein. The solution was injected slowly over five minutes. The routine was combined with that for plasma-volume. A sample of the blood was taken before injection, the syringe was changed and Evans blue injected, the syringe changed again and the thiocyanate injected. Specimens of blood were then taken at regular intervals as described for the plasma-volume method. After the Evans blue in the

serum had been estimated, to 2 c c of serum 2 c c of 15 per cent trichloroacetic acid was added. After mixture, this suspension was centrifuged, and to 2 c c of the supernatant fluid 1 c c of a 5 per cent iron-alum solution added. The resultant coloured solution was compared within 10 minutes in a colorimeter with a similarly treated solution made by diluting the solution used for injection to one part in 4,000. The serum obtained before injection of the thiocyanate was used as a control. The control is essential where repeated

TABLE VII
Extracellular Fluid Volumes in Two Cases

	(a)	(b)
<i>On Admission</i>		
Fluid volume (litres)	19.4	15.4
Percentage of body weight	30.8	20.2
<i>After Exercise—Seven Days</i>		
Fluid volume (litres)	20.5	14.4
Percentage of body weight	32.2	18.2
<i>After Rest—Eight Days</i>		
Fluid volume (litres)	15.0	15.4
Percentage of body weight	25.7	20.2

estimations are made on the same individual, for the thiocyanate ion persists in the blood-stream for seven to 10 days in detectable amounts.

The extracellular fluid volume of five cases after loss of oedema varied between 12.2 and 15.0 litres, constituting from 20 to 28 per cent of body weight. Laviètes, Bourdillon, and Klinghoffer (1936) found individual variations in man of from 17 to 28 per cent of body weight as determined by injection of sulphate, saccharose, and thiocyanate. The changes in extracellular fluid on exercise have been followed from two cases.

As described above, these two cases on admission to hospital were treated on exercise for seven days and then complete rest for eight days. During the period of exercise the first patient, who had well developed oedema on admission, gained one litre of extracellular fluid during exercise and lost 5.5 litres when resting. The second patient, who had minimal oedema, showed no significant change in fluid volume and did not show any change in weight in the two weeks of the experiment. From these figures it appears that the thiocyanate method offers a means of following water-storage changes in cases of famine oedema and might well be used in the study of non-oedematous cases with low plasma-proteins and possible occult oedema.

Urinary Changes in Oedema

The urinary changes that occur in oedema cases on rest in bed have been summarized above, and similar findings have been reported by Schittenhelm and Schlecht (1918), Tonm (1919), Govaerts and Lequime (1942), and many others. During the first two days of rest, volumes of urine as high as five litres per diem were passed. This output was greatly in excess of the fluid

intake. Nocturnal frequency was a marked feature, and the nocturnal volume was at least equal to the volume passed by day. Govaerts and Lequime (1943) used this finding in their cases to explain the development of oedema. They believed that the patient at first passes at night the excess of fluid he has retained during the day's activity. Eventually, fluid retention exceeds the excretory power and fluid accumulates, requiring more and more time in the prone position for its elimination.

A great loss of urinary chloride was associated with the increased diuresis. The amounts of chloride (expressed as gm of chloride ion) lost in the urine per diem for the first five days of rest are shown for four cases in Table VIII.

TABLE VIII
Urine Chloride Output in Four Cases
Chloride (in gm) passed in 24 Hours

1st day	11.2	15.6	28.4	16.1
2nd "	13.3	12.4	17.1	13.8
3rd "	5.7	9.8	10.3	8.7
4th "	7.7	7.3	6.7	6.6
5th "	3.6	2.0	4.0	5.5

As much as 28 gm of chloride may be excreted in 24 hours, as compared with the normal excretion of about 9 gm. After the first few days in bed both the urine volume and the chloride output fall to values much below normal. Thus high urinary output and chloride loss occur while oedema is disappearing. The diminished excretion of chloride from the third day onwards is probably the result of the marked fall in plasma-chloride that occurs during the first five days, as shown in Fig. 3.

Chloride Metabolism and Oedema

In almost all descriptions of hunger oedema the intake of large amounts of water and salt is emphasized. The diet of the cases of the present series was alleged to be deficient in salt, and salt was not part of their rations. They complained of salt lack, but were probably far from salt deficient in view of their high plasma-chloride levels on admission, of the order of 360 mg per 100 c.c., which can be compared with the normal figure 357 given by McCance (1936).

The plasma-chloride changes are shown in Fig. 3. A similar fall in blood-chloride has been described by Maliwa (1917). In the process of losing oedema a large excess of chloride is excreted by the kidneys. The concentrating power of the kidneys for chloride can be examined by studying the ratio of chloride concentration of urine to chloride concentration of plasma. This ratio has been calculated for four cases and is given in Table IX.

From Table IX it is evident that in the first day of rest in bed the kidneys excreted a urine of chloride concentration greater than that of the plasma, in some cases the chloride concentration of the urine was nearly twice that of the plasma. This would deplete the body of chloride and thus

depletion is indicated by a fall in plasma-chloride (Fig 3) For the remaining four days in bed, the ratio fluctuated about a value of one, indicating that the chloride concentration of the urine was essentially that of the plasma During exercise a striking change in the ratio occurred The urine chloride concentration fell below that of the plasma, giving a ratio of less than one In this period when oedema was developing chloride reabsorption

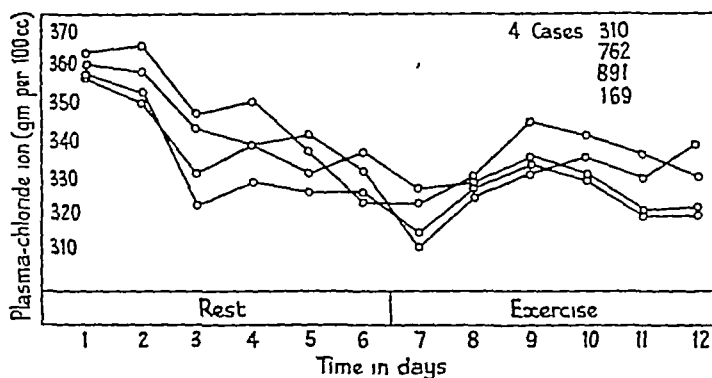


FIG 3 Daily variation in plasma-chloride

TABLE IX

Chloride Concentration of Kidneys in Four Cases

		Ratio $\left\{ \begin{array}{l} \text{Urine Chloride Concentration} \\ \text{Plasma-chloride Concentration} \end{array} \right.$			
Rest in bed	1st day	1 80	1 75	1 41	1 52
	2nd "	1 00	0 91	0 99	1 02
	3rd "	0 90	1 03	0 93	0 85
	4th "	0 96	1 03	1 03	1 34
	5th "	1 08	1 17	1 11	1 11
Exercise	6th "	0 44	0 56	1 02	0 71
	7th "	0 79	0 81	0 87	0 79
	8th "	0 77	0 80	0 78	0 86
	9th "	0 62	0 75	0 61	0 78
	10th "	0 90	0 87	0 97	1 00
	11th "	0 69	0 95	1 39	1 02
	12th "	0 88	0 84	0 73	0 72
Rest in bed	13th "	0 94	0 89	0 77	0 89
	14th "	0 98	1 03	0 91	0 84
	15th "	1 52	1 26	1 36	1 38

by the tubules was increased and chloride retention occurred In the second rest period from the thirteenth to the fifteenth day excess chloride was again excreted to raise the urine chloride concentration above that of the plasma and to give a ratio greater than one These figures lead to the conclusion that while oedema fluid is being excreted the urine contains more chloride than does the oedema fluid, which is the origin of the excess of urine For the excretion of oedema fluid excess chloride appears to be necessary Certainly it has been shown in experimental sodium-chloride deficiency in man (Baltes and Smirk, 1934, McCance and Widdowson, 1937) that ingested

water fails to produce a normal diuresis in the salt-deficient subject. Indeed, Gilman and Goodman (1937) have suggested a system including a hypothalamico-hypophyscal mechanism operating through a sensitivity to the salt-content of the blood and controlling the tubular reabsorption of salts and water.

During exercise, when fluid is retained with the development of oedema, chloride retention can be demonstrated. For the production of oedema in experimental protein deficiency sodium-chloride retention is essential (Kerkhof, 1938), confirming many clinical observations on the development of hunger oedema. These conclusions are supported by the work of McCance (1937) and Lyons, Jacobson, and Avery (1944), who have shown that the water-content of the blood can be lowered by salt deficiency and raised by a free salt intake.

In hunger oedema the main factor in the production of water retention is the lowering of plasma-proteins, but other factors such as the salt intake and urinary excretion or retention of chloride and water are of importance. Disturbance of salt metabolism may alter the glomerular filtration rate, thus altering water excretion, or alternatively electrolyte and water excretion may be independent of the rate of glomerular filtration, but be regulated by tubular absorption. The volume of the glomerular filtrate is always so much greater than the volume of the urine that, unless there are gross variations in the former, the volume of the urine is likely to be unaffected by alterations in glomerular flow (Barclay and Cooke, 1944). From the figures given in Table IX it appears that during exercise retention of chloride occurs as a result of tubular reabsorption, and conversely during rest an excess of chloride is excreted as a result of diminished reabsorption of the ion. That exercise exerts an influence on the renal tubules is apparent, although the mechanism by which the changes are produced remains unexplained. The urinary changes produced in hunger oedema cases by changes in physical activity offer a promising field for investigation of renal function, and an examination of glomerular and tubular activity in these cases might provide a useful approach to the problems of chloride and water metabolism.

Summary

1 Total plasma-proteins are decreased in oedema cases. Mean values of 5.24 gm per 100 c.c. of plasma in slight cases, 5.07 in moderate cases, and 4.90 in severe cases were obtained as compared with 7.04 gm per 100 c.c. for a normal control group. Plasma-albumen values in 14 oedema cases ranged from 2.58 to 3.81 gm per 100 c.c. of plasma. The lowered plasma-proteins are believed to result in the accumulation of oedema that commences with the first lowering of the protein level. The view that there is a critical level of plasma-protein for the production of oedema is not accepted.

2 Plasma-volumes determined by the Evans blue method give values from 1.74 to 3.30 litres per sq. metre of body surface. High values were

obtained while oedema was present, and where the examination was repeated after loss of oedema the plasma-volume fell to normal. This fall in plasma-volume was associated with haemoconcentration as shown by a rise in haemoglobin and plasma-protein. This was taken to indicate that hydraemia occurs in hunger oedema.

3 Four cases of apparently cured oedema were exercised with reappearance of the oedema. Two cases with oedema were exercised while on full diet with persistence of the oedema until the patients were allowed complete rest. Exercise appears to be a potent factor in the production and retention of oedema.

4. Daily plasma-protein determinations on oedema cases showed a diurnal variation which was probably due to variation in the degree of hydration of the blood.

5 The inaccuracy of the clinical assessment of oedema is illustrated by a patient showing minimal oedema who lost $8\frac{1}{2}$ litres of oedema fluid. This case is contrasted with another showing severe oedema, but losing only two litres of oedema fluid. It is shown that much excess fluid may be hidden in the deeper connective tissues of the mediastinum and abdomen.

6 The extracellular fluid volumes have been determined by the thiocyanate method and in non-oedematous cases ranged from 20 to 28 per cent. of body weight. Extracellular fluid volume is shown to decrease in loss of oedema.

7 Urinary chloride excretion was high during loss of oedema. While as much as 28 gm of chloride were being lost per diem, the kidney excreted a urine of chloride concentration greater than that of the plasma, with resultant fall of plasma-chloride concentration. During periods of exercise while oedema fluid is collecting, the urinary chloride concentration is less than that of the plasma, indicating chloride retention. These changes are believed to be the result of tubular activity.

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THE OEDEMATOUS SYNDROME OF NEPHRITIS WITH SPECIAL REFERENCE TO PROGNOSIS¹

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THIS paper is principally concerned with the fate of patients suffering from that form of Bright's disease characterized by persistent oedema and very heavy proteinuria. Most authorities consider this syndrome a phase of chronic glomerulo-nephritis, which sometimes develops in the transition from the acute or initial stage to the terminal uraemia. Terms such as the active chronic stage of haemorrhagic Bright's disease, subacute or chronic parenchymatous nephritis, chronic nephritis with oedema, or the nephrotic syndrome of chronic nephritis, have all been employed by those who hold that opinion. There is an alternative view that the oedematous syndrome is not secondary to an attack of acute nephritis, but is a separate variety of glomerulo-nephritis (Longcope, 1938, Ellis, 1942). The evidence which led these authors to this belief may be summarized as follows. Firstly, in patients with the oedematous syndrome, no history of an attack of acute nephritis was obtained, and in no instance did the syndrome develop in patients who had been kept under observation for years after an attack of acute nephritis. Secondly, acute nephritis was usually preceded by an infection, the onset was sharp, the course short, and the outcome as a rule favourable. The reverse was the case with the oedematous syndrome. Thirdly, the serological studies of Longcope (1938) and his colleagues indicated that infection with haemolytic streptococci had occurred in over 90 per cent of patients with acute nephritis, but only rarely in those with the oedematous syndrome. Fourthly, from his extensive studies Ellis (1942) concluded that the renal histology was quite distinctive from that of acute nephritis and its sequelae.

Whatever view is taken as to the pathogenesis of the oedematous syndrome, the cases comprising it appear to be clinically divisible into two groups. In one, which is much the larger, the oedema is accompanied by haematuria from the start, and hypertension and azotaemia, if not present initially, appear later, and death eventually results from uraemia. In the other and much smaller group, haematuria, hypertension, and azotaemia are said to remain absent throughout the entire course of the disease, and to this group the term lipoid or pure nephrosis is applied to denote a separate, primarily degenerative condition in which the prognosis is claimed to be good if the patient survives intercurrent infection. In this group complete recoveries have been recorded, after prolonged periods of observation, by Aldrich (1930),

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Bannick (1934), Tappan (1935), Schwarz and Kohn (1935), and Oertel (1939). On the other hand, notwithstanding the number of recoveries recorded, it is becoming increasingly recognized that many cases, diagnosed initially as pure nephrosis, may later show haematuria, hypertension, or azotaemia, and die of uraemia (Bannick, 1934, Major, 1936, Fahr, 1937, Ellis, 1942). Fishberg (1939), who followed cases of pure nephrosis for a year or more after the disappearance of oedema and during which time albuminuria was the only abnormality, never saw complete cure. Ellis (1942) did not consider pure nephrosis an entity separate from the oedematous syndrome which he regarded as running a progressive course to uraemia. He observed only five complete recoveries in 145 cases. Schwarz and Kohn (1935) found that eight out of 40 patients with pure nephrosis were entirely recovered 15 years after the onset of the illness, but a further review five years later (Schwarz, Kohn, and Weiner, 1943) showed that four of the eight then showed hypertension and intermittent albuminuria.

In view of the conflicting findings as to the prognosis, the primary object of the work recorded in the present paper was to review the course of the oedematous syndrome in 29 patients and to determine, by clinical and biochemical investigation, the functional state of the kidneys in the survivors.

Methods

Plasma proteins (Howe, 1921, modified by Hawk and Bergeim, 1938)

Plasma-cholesterol (Bloor and Knudson, 1916, 1917)

Plasma non-protein nitrogen (Folin and Wu, 1919)

Blood urea (Archer and Robb, 1924)

Urea clearance (Peters and Van Slyke, 1931)

Fluctuations in oedema were gauged by daily weighing

Clinical Observations

In Table I are set out the more important clinical and biochemical data on 29 cases of the oedematous syndrome at the time of their first examination. The Wassermann reaction was negative in every instance.

History. As the onset of the illness was insidious in almost all the patients, the appearance of oedema was taken to mark the start of the disease. This is admittedly fallacious (Ellis, 1942), and in my own experience albuminuria was detected by chance in Case 27, six weeks before the appearance of oedema. In 28 of the patients no previous history of Bright's disease was obtained prior to the onset of the illness. The remaining patient, Case 10, had had scarlet fever a year before the appearance of the oedematous syndrome. Although there was slight albuminuria at the height of the fever, the physician in charge did not consider that nephritis was present. Five of the 29 patients (17 per cent) had an acute infection within three weeks of the onset of oedema, four complaining of a cold or chill after a wetting, and one of influenza. None of the patients gave a history of headache, backache, or vomiting at the time of the appearance of oedema.

TABLE I

Initial Observations on 29 Cases of the Oedematous Syndrome

Case number	Age (years)	In plasma					Systolic blood-pressure (mm Hg)	Blood in urine	Duration of oedema (weeks)
		Total protein (gm per 100 c.c.)	Albumin (gm per 100 c.c.)	Globulin (gm per 100 c.c.)	Non-protein nitrogen (mg per 100 c.c.)	Cholesterol (mg per 100 c.c.)			
1	7	6.86	2.47	4.39	27.2	—	104	0	30
2	4	5.06	2.41	2.65	28.0	—	90	0	2
3	9	2.06	2.86	31.3	31.3	—	93	0	1
4	11	4.68	2.21	2.47	25.0	536	100	0	16
5	15	4.74	2.25	2.40	24.2	538	116	0	9
6	17	3.17	1.17	2.06	34.2	—	112	0	2
7	40	5.38	1.56	3.82	35.0	334	120	0	1
8	8	2.45	1.63	2.72	27.2	—	90	0	100+
9	45	3.77	1.71	2.06	34.2	—	112	0	4
10	11	4.67	1.42	3.25	54.7	—	110	0	2
11	41	4.42	1.79	2.63	47.5	725	145	M	5
12	33	4.61	2.42	2.19	24.5	—	155	M	70
13	16	3.96	1.92	2.04	19.0	—	150	M	1
14	12	4.71	1.91	2.80	56.0	615	118	M	2
15	8	5.36	2.12	3.24	36.1	—	107	M	12
16	9	6.22	2.48	3.74	50.0	—	118	+	1
17	7	4.36	1.92	2.44	36.7	—	100	M	4
18	11	5.08	1.71	3.37	33.3	—	90	M	2
19	10	5.41	2.74	2.67	35.3	—	136	M	4
20	6	4.71	1.81	2.90	87.0	—	120	M	62+
21	4	4.41	2.03	2.38	40.0	—	125	M	32
22	6	4.23	1.66	2.57	74.0	—	132	M	5
23	10	5.47	2.40	3.07	22.0	1,080	142	+	4
24	23	5.11	2.74	2.37	58.0	—	118	M	27
25	47	5.23	2.55	2.68	29.7	760	150	M	4
26	19	4.52	2.83	1.69	29.9	410	145	0	3
27	25	3.66	2.16	1.50	33.3	—	182	M	78
28	61	4.84	2.78	2.06	39.0	598	160	+	6
29	36	4.35	2.65	1.70	28.0	397	180	+	29
30									8

M = Red blood cells present on microscopic examination

+ = Guaiac reaction positive

Bannick (1934), Tappan (1935), Schwarz and Kohn (1935), and Oertel (1939) On the other hand, notwithstanding the number of recoveries recorded, it is becoming increasingly recognized that many cases, diagnosed initially as pure nephrosis, may later show haematuria, hypertension, or azotaemia, and die of uraemia (Bannick, 1934, Major, 1936, Fahr, 1937, Ellis, 1942) Fishberg (1939), who followed cases of pure nephrosis for a year or more after the disappearance of oedema and during which time albuminuria was the only abnormality, never saw complete cure Ellis (1942) did not consider pure nephrosis an entity separate from the oedematous syndrome which he regarded as running a progressive course to uraemia He observed only five complete recoveries in 145 cases Schwarz and Kohn (1935) found that eight out of 40 patients with pure nephrosis were entirely recovered 15 years after the onset of the illness, but a further review five years later (Schwarz, Kohn, and Weiner, 1943) showed that four of the eight then showed hypertension and intermittent albuminuria

In view of the conflicting findings as to the prognosis, the primary object of the work recorded in the present paper was to review the course of the oedematous syndrome in 29 patients and to determine, by clinical and biochemical investigation, the functional state of the kidneys in the survivors

Methods

Plasma proteins (Howe, 1921, modified by Hawk and Bergeim, 1938)

Plasma-cholesterol (Bloor and Knudson, 1916, 1917)

Plasma non-protein nitrogen (Folin and Wu, 1919)

Blood urea (Archer and Robb, 1924)

Urea clearance (Peters and Van Slyke, 1931)

Fluctuations in oedema were gauged by daily weighing

Clinical Observations

In Table I are set out the more important clinical and biochemical data on 29 cases of the oedematous syndrome at the time of their first examination The Wassermann reaction was negative in every instance

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still oedematous, two years after the onset. Five patients who had no azotæmia on admission to hospital are known to have developed nitrogen retention and four of them have died in uræmia (Cases 12, 19, 23, and 25).

Hypercholesterolaemia The plasma-cholesterol was estimated in 10 cases (Table I) and was well above normal in every instance.

Hypoproteinaemia All 29 patients at the time of their admission to hospital showed hypoproteinaemia due to a fall in plasma-albumin, which

TABLE II

Hepatic Function in the Oedematous Syndrome

Case number	Plasma-laevulose (after 50 gm by mouth) (mg per 100 c c)		Cephalin flocculation	Benzoic acid in 4 hr in urine (gm)	In plasma	
	$\frac{1}{2}$ hr	1 hr			Albumin (gm per 100 c c)	Globulin (gm per 100 c c)
5	11.6	12.7	Negative	3.1	2.25	2.49
7	7.3	7.3	"	3.6	1.56	3.82
11	8.5	8.0	"	3.4	2.20	1.80
13	9.1	8.2	"	3.3	1.53	2.56
28	10.2	11.2	"	3.0	2.78	2.0
29	10.8	15.2	"	3.5	2.20	1.0

was invariably less than 3.0 gm per 100 c c (Table I). In 23 patients it was less than 2.5 gm and in 11 less than 2.0 gm per 100 c c. The plasma-globulin was greater than 3.0 gm per 100 c c in seven cases. The presence of infection could not be demonstrated at the time of these observations, and no explanation for this hyperglobulinaemia is offered.

Hypoalbuminaemia in relation to hepatic function Broadly speaking, hypoalbuminaemia is believed to result from three causes, deficient intake or defective absorption of nitrogen as seen in nutritional oedema or cachectic states, excessive loss of serum-albumin as in burns or prolonged albuminuria, and defective synthesis as in cirrhosis of the liver. Absorption of adequate protein cures the hypoalbuminaemia of starvation within a few weeks, but is without effect in the oedematous syndrome or cirrhosis of the liver, even if a positive nitrogen balance be maintained for a long period. It has therefore been suggested (Loeb, 1941) that failure to synthesize plasma-albumin by patients with the oedematous syndrome may be due, in part at least, to a hepatic defect. In an attempt to verify this hypothesis, the laevulose tolerance test (Rennie, 1943), the cephalin cholesterol flocculation test (Hanger, 1939), and the hippuric acid synthesis test (Probstein and Londe, 1940), were performed on six patients (Table II).

The results obtained gave no confirmation that hepatic dysfunction was present, since laevulose tolerance and hippuric acid synthesis were not impaired and the cephalin flocculation test was negative.

Course

In Table III are summarized the results of a survey made on the 29 cases of the oedematous syndrome in the first six months of 1946. All who are

Age Since 13 cases were seen at the Royal Hospital for Sick Children, where the age-limit for admission is 13 years, and 16 at the Western Infirmary, where patients of all ages are taken, no inference can be drawn as to age distribution. The age of the patients ranged from four to 60 years at the time of the appearance of oedema, and seven were over 40 years of age.

Sex Twenty out of 29 patients (69 per cent) were male.

Oedema Oedema was present in all patients at the time the observations in Table I were made. It was well marked and usually accompanied by ascites. Persistence of oedema in spite of treatment was the rule. It was present for six months or more with seven exceptions. Of these exceptions five died of uraemia or intercurrent infection while still oedematous. Two lost their oedema after three and five months respectively and now show normal blood chemistry and renal function (Cases 5 and 11).

Hypertension Hypertension of slight or moderate degree was considered to be present in 14 patients (Cases 11 to 13, 16, 19 to 23, and 25 to 29), six of whom were seen in the first five weeks of their illness. In all 14 hypertension persisted. Eight have died of uraemia, and in five the course of the disease is stationary or progressive. One patient only has improved, 18 months after the onset there is no oedema and the blood chemistry and renal function are normal, but there is still slight albuminuria and the blood-pressure is 145/90 mm Hg.

Haematuria Frank blood in the urine giving a positive guaiac reaction was observed in four patients when first seen (Table I), and red blood cells were found on microscopic examination in a further 13. Of the four patients with frank haematuria, two died of uraemia within a year and two are unchanged, having had oedema for eight and 13 months respectively. Complete recovery has not been observed so far in any of the 13 patients who showed microscopic haematuria, whereas in the three patients in the series who now appear to be well haematuria was never detected. Absence of haematuria, however, was not necessarily indicative of a good prognosis, since five patients without haematuria on admission developed it subsequently. Two of these died of uraemia and one shows progressive impairment of renal function.

Laboratory Investigations

Azotaemia As measured by a rise of the non-protein nitrogen of the blood above the normal upper limit of 40 mg per 100 c.c., azotaemia was present in eight out of 29 patients on admission to hospital (Table I). All but one were in the first five weeks of illness. In five azotaemia persisted till death in uraemia after an illness of less than a year. In the remaining three patients an elevation of non-protein nitrogen was noted only at the time of the first observation, and normal results were obtained on numerous occasions subsequently. Two of these (Cases 11 and 14), except for abnormality of the urine, are otherwise normal 13 months and six years respectively after the onset of nephritis. The third (Case 10) died of intercurrent infection, while

still oedematous, two years after the onset. Five patients who had no azotæmia on admission to hospital are known to have developed nitrogen retention and four of them have died in uræmia (Cases 12, 19, 23, and 25).

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The results obtained gave no confirmation that hepatic dysfunction was present, since laevulose tolerance and hippuric acid synthesis were not impaired and the cephalin flocculation test was negative.

Course

In Table III are summarized the results of a survey made on the 29 cases of the oedematous syndrome in the first six months of 1946. All who are

still alive have been interviewed and examined. Inquiries into the cause of death were made in seven instances when it had occurred in the patient's home or in another hospital.

Death from uraemia Death from this cause was the most frequent in the series, occurring in 12 patients from four months to six years after the appearance of oedema. Oedema, accompanied by hypoalbuminaemia, was observed to persist until death in seven, but in two (Cases 23 and 24) it

TABLE III

*Fate of 29 Patients with the Oedematous Syndrome**

Years since onset	Died of uraemia	Died of intercurrent infection	Recovery	Much improved	Improved	Unchanged or worse
1	5	2	—	—	1	1
1 to 2	4	1	—	—	1	2
2 " 3	—	—	—	—	1	—
3 " 4	1	—	—	—	—	1
4 " 5	—	—	—	—	—	—
5 " 6	2	—	—	1	—	1
6 " 7	—	—	1	—	—	—
12 " 15	—	—	2	1	—	—
Totals	12	3	3	2	3	5

* One patient not shown in the table died suddenly after intravenous injection of a mercurial diuretic (Rennie, 1945)

Recovery = No abnormality detected

Much improved = Faint trace of albumin in urine, no casts or red blood cells

Improved = Albuminuria with red blood cells and casts

Unchanged or worse = Albuminuria, &c, abnormal blood chemistry, hypertension, oedema

disappeared and the plasma-albumin returned to normal limits after six and seven months respectively. A boy of nine years (Case 23) lived for 30 months longer, and during the major part of this time the blood-urea was never less than 80 mg per 100 c.c. Eleven months before death his appendix required to be removed and this was done without incident, although his blood-urea at the time was 115 mg per 100 c.c. Death in the remaining three cases took place at home or in another hospital, but from information supplied by the doctors in attendance it is reasonably certain that the cause was uraemia. Oedema was present at death in all three.

Death due to intercurrent infection Death from this cause was observed on three occasions. Case 6 died of cellulitis of the leg, which gave rise to septicaemia, and Cases 2 and 10 of pneumococcal peritonitis.

Recovery Three patients (Cases 3, 4, and 8) appear to have recovered completely (Table IV). None showed oedema, the urine was clear, and the blood-pressure, urea clearance, and plasma-albumin were within normal limits. The plasma-cholesterol was slightly above normal in Cases 3 and 4. Case 3, a boy of nine years, showed oedema from September 1938 to the end of 1940. From that time he was seen at intervals of six months, and albuminuria was observed to become progressively less and disappear at the end of 1945. In 1946 he was passed grade A1 by a Recruiting Medical

Board, but was discharged from the Army on my representation to the authorities. Case 4, a girl aged nine years, was oedematous for eight months in 1933. She was not seen again until 1946, when it was learned that she had returned to school in 1935 and had worked regularly since leaving at 14 years. She had married in June 1946. Case 8, a girl of seven years, was oedematous from September 1930 till November 1932. Thereafter albuminuria persisted for seven months till May 1933. At that time the blood

TABLE IV
Recovery from the Oedematous Syndrome

	Case 3		Case 4		Case 8	
	1938	1946	1933	1946	1930	1946
Oedema	+++	0	+++	0	+++	0
Albuminuria	+++	0	+++	0	+++	0
Haematuria	0	0	0	0	0	0
Systolic blood-pressure (mm Hg)	100	128	90	120	108	130
Plasma albumin (gm per 100 c c)	2.21	4.94	2.06	4.73	2.45	4.66
Plasma-cholesterol (mg per 100 c c)	586	274	—	260	—	219
Plasma non-protein nitrogen (mg per 100 c c)	25.2	29.0	31.3	29.8	27.2	27.0
Urea clearance (per cent of normal)	94	108	—	101	—	101
Water concentration test (specific gravity)	—	1028	—	—	—	1026

TABLE V
Present State of Patients Much Improved

Case number	14	18
Oedema	0	0
Albuminuria	Very faint trace	Very faint trace
Haematuria	0	0
Systolic blood-pressure (mm Hg)	115	122
Plasma-albumin (gm per 100 c c)	4.39	5.18
Plasma-cholesterol (mg per 100 c c)	242	273
Plasma non-protein nitrogen (mg per 100 c c)	33	31
Urea clearance (per cent of normal)	115	77
Duration (years)	6	14

chemistry was normal and the systolic blood-pressure 120 mm Hg. This patient has also been at work regularly.

Much improved. Two patients (Cases 14 and 18 in Table I) when re-examined six and 14 years respectively after the onset of the disease showed a very faint trace of albumin in the urine (Table V). Red blood cells were not seen. The urea clearance and blood-pressure were normal. With the exception of a slightly increased plasma-cholesterol in Case 18, blood chemistry was also normal. Case 14, a boy of 13 years, when first seen in 1940 had had oedema for 11 months. During the following five years he was well save for albuminuria which became a trace in 1945. In 1946 he was passed fit for military service overseas, but on representation to the authorities he was released from the service. Case 18, a girl of 11 years first seen in 1932, was oedematous for 18 months. In 1934 there was no oedema, but albuminuria was considerable and a few red blood cells were present in the urine. She returned to school in the same year, and worked regularly in a munition factory throughout the war. Both patients had haematuria when first seen,

and Case 14 also showed slight azotaemia once, on admission, but as in the previous group who appear to have recovered, hypertension was never detected

Improved Three patients (Cases 5, 7, and 11 in Table I) who have been under continuous observation for shorter periods than those in the two foregoing groups, had no oedema but showed moderate albuminuria and scanty casts (Table VI) Two had, in addition, microscopic haematuria, Case 7 had

TABLE VI
Present State of Patients Improved

Case number	5	7	11
Oedema	0	0	0
Albuminuria	Trace	+	Trace
Haematuria	Microscopic	0	Microscopic
Systolic blood pressure (mm Hg)	110	118	145
Plasma albumin (gm per 100 c c)	4.80	3.85	4.48
Plasma-cholesterol (mg per 100 c c)	—	130	142
Plasma non-protein nitrogen (mg per 100 c c)	29	20	37
Urea clearance (per cent of normal)	78	124	76
Duration (years)	2	1	2

TABLE VII
Present State of Patients Unchanged or Worse

Case number	13	26	27	28	29
Oedema	+	0	0	+++	+++
Albuminuria	+++	++	++	+++	+++
Haematuria	Micro- scopic	Micro- scopic	Micro- scopic	+	+
Systolic blood pressure (mm Hg)	160	175	210	155	150
Plasma albumin (gm per 100 c c)	2.44	3.53	3.01	2.50	2.29
Plasma cholesterol (mg per 100 c c)	416	228	250	342	333
Plasma non-protein nitrogen (mg per 100 c c)	26	35	30	51.0	25
Urea clearance (per cent of normal)	65	58	56	43	50
Duration (years)	2	5	4	2	1

slight hypoalbuminaemia, and Case 11 slight hypertension. None showed azotaemia, and all had normal urea clearances and blood-pressures. On admission Cases 5 and 7 fell into the category of pure nephrosis, but subsequently developed haematuria. Case 11 showed haematuria on admission and also slight azotaemia and hypertension.

Unchanged or worse In this category are placed five patients (Table VII) whose condition is stationary (Cases 13, 28, and 29) or who have deteriorated (Cases 26 and 27). At the time of the last examination all showed hypertension, haematuria, and gross albuminuria. All had a plasma-albumin level below 4.0 gm per 100 c c, associated, when below 3.0 gm per 100 c c, with oedema and hypercholesterolaemia. The urea clearance was below normal in four patients and at the lower limit of normal in the fifth. Cases 13, 28, and 29, during the short period of observation, have shown little change. Cases 26 and 27 have deteriorated. Although oedema has disappeared and the plasma-albumin has tended to rise, the urea clearance has diminished and hypertension has increased (compare with

Table I) When first seen all these patients had hypertension which has persisted or increased

Discussion

Nine out of 29 patients when first seen (five within two weeks of the appearance of oedema) showed the clinical syndrome to which the term pure nephrosis has been given. The subsequent appearance of haematuria in two and the death in uraemia of a third is in agreement with the findings of others that the diagnosis of pure nephrosis frequently requires revision. Nevertheless, the only examples of what appear to be complete cures in the series of 29 patients were observed in three who had never shown hypertension, haematuria, or azotaemia. In the light of the report of Schwarz, Kohn, and Weiner (1943) that albuminuria recurred and hypertension appeared five years after apparent recovery from pure nephrosis and 20 years from the beginning of the illness, it may well be that the period of observation in the patients reported in the present paper is too short to justify the opinion that permanent cure is established. It is fair to conclude that even if renal failure is eventually to occur in all patients with the oedematous syndrome, the process is very much slower in those whose clinical picture is initially that of pure nephrosis.

With regard to the significance of individual manifestations, azotaemia, if persistent, heralded the early appearance of uraemia. The best early indication of a progressive renal lesion, however, was hypertension. Of 14 patients who showed an elevation of blood-pressure when first examined (eight in the first eight weeks of their illness) eight died in uraemia and only one of the rest has improved. In no single one did the blood-pressure return to normal. On the other hand, of the 15 patients who showed no hypertension when first examined (10 in the first eight weeks of their illness) only four have died of uraemia and seven are well or improved. Four died of intercurrent incidents. Ellis (1942) found that when blood-pressure was very high initially, renal failure followed rapidly, but if the hypertension was slight or moderate the blood-pressure sometimes returned to normal for a time and the disease ran a more chronic course. In the present series of cases a slight degree of hypertension proved to be ominous even in the absence of azotaemia or haematuria.

It is well recognized that intercurrent infection is a frequent and often fatal complication of the oedematous syndrome. In the present series of 29 cases two patients died of pneumococcal peritonitis and one of septicaemia arising from cellulitis of an oedematous leg. A fairly high proportion of the deaths was therefore due to intercurrent infection. On the other hand, it has been recorded by Aldrich (1926), Gautier (1933), and others that intercurrent infection may be followed by great improvement or even cure. Fishberg (1939) stated that the improvement as a rule is limited to the temporary disappearance of oedema. Intercurrent attacks of paratyphoid fever, measles, and chickenpox respectively had no effect, one way or the

other, upon the course of the disease in three of my patients. A fourth developed pneumonia which was complicated by empyema. Oedema at the same time disappeared, but albuminuria continued unchanged, and some weeks after resection of a rib oedema returned. This was one of the two patients who died of pneumococcal peritonitis, which developed four months after the empyema. In the present series of cases intercurrent infection did not have a favourable effect upon the disease.

Summary

1 The pathogenesis of the syndrome of Bright's disease characterized by protracted oedema and albuminuria is briefly discussed.

2 Twenty-nine patients with this syndrome have been observed during the past 16 years. In none was a history of acute nephritis obtained.

3 The clinical and biochemical changes on admission to hospital are described.

4 In 1946, 13 patients were alive. Three appeared to be well in every respect seven, 13, and 15 years from the appearance of oedema, and two, six and 14 years afterwards, showed a very faint trace of albumin in the urine as the sole abnormality. Three patients, although free of oedema, showed more marked albuminuria and microscopic haematuria. Of the remaining five, three were still oedematous and two, although free of oedema, were showing increasing hypertension.

5 Sixteen patients had died, 12 of uraemia, three of intercurrent infection, and one after an intravenous injection of a mercurial diuretic.

6 All three recoveries were noted in patients in whom hypertension, azotaemia, and haematuria were not observed.

7 Hypertension was the best early indication of a progressive lesion. Out of 14 patients with hypertension when first seen, eight died of uraemia and only one of the remainder improved.

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2 Twenty-nine patients with this syndrome have been observed during the past 16 years. In none was a history of acute nephritis obtained.

3 The clinical and biochemical changes on admission to hospital are described.

4 In 1946, 13 patients were alive. Three appeared to be well in every respect seven, 13, and 15 years from the appearance of oedema, and two, six and 14 years afterwards, showed a very faint trace of albumin in the urine as the sole abnormality. Three patients, although free of oedema, showed more marked albuminuria and microscopic haematuria. Of the remaining five, three were still oedematous and two, although free of oedema, were showing increasing hypertension.

5 Sixteen patients had died, 12 of uraemia, three of intercurrent infection, and one after an intravenous injection of a mercurial diuretic.

6 All three recoveries were noted in patients in whom hypertension, azotaemia, and haematuria were not observed.

7 Hypertension was the best early indication of a progressive lesion. Out of 14 patients with hypertension when first seen, eight died of uraemia and only one of the remainder improved.

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OSTEOMALACIA WITH LOOSER'S NODES (MILKMAN'S SYNDROME) DUE TO A RAISED RESISTANCE TO VITAMIN D ACQUIRED ABOUT THE AGE OF 15 YEARS¹

By R A McCANCE

(From the Department of Experimental Medicine, Cambridge)

With Plates 1 to 4

THERE are many aspects of calcium metabolism and vitamin D activity which are still undescribed, much less understood. The purpose of the present article is to give an account of the investigation and cure of an unusual abnormality of metabolism, to discuss the findings with reference to the literature, and finally to draw attention to an unrecognized feature of vitamin D metabolism which must be taken into account in any complete description of its activity.

Case Report

D L was born in 1922 and is the daughter of healthy parents. She has one sister, who is healthy. Her birth and infancy were normal, and at school she distinguished herself at both games and athletics and won the school high jump when she was 14. During her 15th year she noticed that her left ankle was weak and that in consequence she was limping a little, but this did not prevent her obtaining a post as a shorthand typist when she was 15½. During the next year people began to remark on her gait and she became so weak that she had difficulty in getting up from an armchair. In 1939, when she was 17, she was admitted to Maida Vale Hospital for Nervous Diseases. At that time she was described as having a rolling gait, but walking had become extremely painful and almost impossible. Her muscles, moreover, had become very weak, and at times she could scarcely raise her head and shoulders from the bed. An X-ray photograph of her lumbar and sacral region was taken at this time and was passed as normal, but, looking at it in the light of subsequent photographs, it is easy to see that bony changes were already quite advanced (Plate 1, Fig 1a). A diagnosis of primary muscular dystrophy was made on the clinical findings and the creatine/creatinine ratio in the urine (Table I), and the girl was treated with physiotherapy and large doses of glycine. She appeared to have improved slightly by the time she was discharged.

In the next two years her weakness and pain became worse, and in 1941, at the age of 18½ years, she was admitted to the Royal National Orthopaedic Hospital, where a double diagnosis was entertained. She was described as having a myopathy leading to extreme muscular weakness without muscular

¹ Received October 7, 1946

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wasting and a condition resembling osteomalacia with advanced decalcification of the skeleton and deformities of her pelvis. Her serum-phosphorus was low and serum-calcium normal (Table I). Her red cells numbered 4,500,000 per c mm, her haemoglobin was 90 per cent, and her colour-index 1.0. Her Wassermann reaction was negative. She is stated to have shown a positive Chvostek's sign, but, in view of her normal serum-calcium and the failure of subsequent investigators to elicit this sign, this may not have been correct.

She was next admitted to the Middlesex Hospital. Further tests of her serum chemistry were made (Table I), and the X-ray photographs which were taken demonstrated still further decalcification, with spontaneous fractures in one ulna and the pelvic bones, and extreme coxa vara. An unusual bony defect was also detected in the right femur (Plate 3, Fig 2). Her skull was said to be normal. Her chief complaint at that time was of pain in her bones. Early in 1942 she was transferred for a time to the Stoke Mandeville Emergency Hospital, where she was treated with a high vitamin diet, calcium, sunlight, and physiotherapy. She progressed favourably, and in time was able to walk. According to the patient herself, she was at first given 15 capsules of halibut liver oil daily, but this was gradually reduced to three capsules daily before she was discharged. Each capsule probably contained something of the order of 500 i u of vitamin D, so that this dose would have, or might have, been about 7,500 units daily at the beginning and 1,500 units daily at the end. However, as X-rays still revealed very extensive decalcification, it was not considered advisable to allow her to be up and about. During this period small quantities of some reducing substance were noticed in the urine from time to time. A number of investigations were carried out in 1942-3. Her plasma-bicarbonate ranged from 55 to 71 volumes per 100 c c. A fractional test meal revealed free hydrochloric acid and no abnormality. On May 8, 1943, her blood-sugar was 80 mg per 100 c c fasting, and 130, 130, and 105 mg per 100 c c $\frac{1}{2}$, 1, and $1\frac{1}{2}$ hours after 50 gm of glucose. No sugar was detected in the urine during this test. A dried sample of her faeces was found to contain 16.7 gm of fat per 100 gm. Her blood-urea was 20 mg per 100 c c and her Wassermann reaction again found to be negative. Her parathyroids were explored with a completely negative result and she was finally diagnosed as a case of Fanconi's syndrome.

After a period of treatment as an out-patient at the Middlesex Hospital she was admitted to the Royal Hospital, Wolverhampton, in August 1944. Examination there revealed a rickety rosary, some anterior bowing of the sternum, a severe kyphosis with angulation at the level of D6, and lordosis in the lumbar region with tenderness over the spine of L5. There was a large hard lump about 12 cm long arising from the distal third of the shaft of the right femur, and overlying the bony defect (Plate 3, Fig 2). X-rays showed a generalized decalcification with multiple symmetrical pseudo-fractures (Plates 1, 3, and 4, Figs 1b, 3a, and 4a). She was treated with calcium lactate, syrup of calcium lactophosphate, and 2,000 i u of vitamin D daily, and after a time improved enough to be able to hobble about with crutches and an abdominal support. Her serum chemistry was essentially unchanged and is shown in Table I.

Studies at Cambridge On May 28, 1945, she was admitted to Addenbrooke's Hospital. The clinical and radiological findings which have just been described were corroborated and no significant changes were detected in her serum chemistry (Table I). No sugar, however, was found in her urine. She was

TABLE I

Summary of the relevant serum and urine chemistry and treatment

Date	Hospital	Serum			Urine creatinine ratio	Treatment and operations 'Large doses' of glycine, and physiotherapy
		Calcium (mg per 100 c.c.)	Phosphorus (mg per 100 c.c.)	Phosphatase (units)		
1939	Maida Vale Hospital for Nervous Diseases	—	—	—	1.25	
1941	Royal National Orthopaedic Hospital	10.5	2.1	23 (normal 3-13)	—	
1942	Middlesex Hospital	10.0	1.9	—	—	
April 1942	"	10.2	1.8	—	—	
May 1943	"	9.9	1.9	—	—	
September 1944	Royal Infirmary, Wolverhampton	9.0	1.8	20*	—	Parathyroids explored, but no abnormality detected. About 5,000 i.u. vitamin D daily
November 1944	"	10.03	1.69	—	—	About 2,000 i.u. vitamin D daily
January 1945	"	10.56	1.99	13.6*	—	
May 1945	Addenbrooke's Hospital	10.3	2.1	9.1†	—	500,000 i.u. vitamin D daily (total 21,000,000 units) Biopsy of left humerus Removal of tumour from right femur
June 16-July 27 1945	"	—	—	—	—	
July 1945	"	—	5.1	10.3†	—	
October 1945	"	10.8	4.5	10.5†	—	
November 1945	"	—	—	—	1.30	
December 1945	"	10.0	4.7	5.9†	—	
March 1946	"	11.0	3.9	2.75†	—	
July 1946	"	—	—	—	1.20	

* King-Armstrong units (normal 4 to 12)

† Bodansky units (normal 2 to 6)

[23
55]

given a full hospital diet and exactly one pint of milk a day, and after a preliminary period of about 10 days her intake and output of calcium were measured over a period of seven days. McCance and Widdowson (1942) have described the full technical procedure by which this and the subsequent tests were made. The girl was found to be in negative calcium balance and negative phosphorus balance (Table II). There was in fact somewhat more calcium in her faeces than there had been in her food, so that she was evidently absorbing even less calcium than her intestinal secretions contained. A number of diagnoses were considered. She had been admitted with the diagnosis of Fanconi's (1936) syndrome, which is characterized by generalized decalcification, a low serum-phosphorus, renal glycosuria, and sometimes cystinuria (McCune, Mason, and Clarke, 1943). The essential lesion seems to be a failure of the renal tubules to reabsorb phosphates. It was thought unlikely that the girl was suffering from this metabolic abnormality because it had not shown itself till she was 16, and also because in 1945 she certainly had no renal glycosuria. Her multiple spontaneous idiopathic symmetrical pseudofractures were clearly the bony lesions described by Fromme (1919), Looser (1920 *a, b*), Milkman (1930, 1934), and many others (Michaëlis, 1932, Debray, Thomann, and Gircaux, 1933, dall'Acqua, Levi, and Bordoli, 1936, Garcin, Legrand, and Bernard, 1937, Leedham-Green and Golding, 1937, Roger and Huguet, 1938, Monier-Vinard, 1940), but it is now clear (Camp and McCullough, 1941, Lafitte and Gros, 1942) that these appearances are not characteristic of any one disease, so they scarcely constitute a diagnosis. Her healthy upbringing and her dietary history excluded any question of osteomalacia due to hunger or malnutrition, but the levels of phosphorus and calcium found with such regularity in her serum (Table I) resembled those found in rickets, particularly resistant rickets, and suggested a vitamin D deficiency. It could, however, clearly be no ordinary deficiency, for she had been treated quite generously with vitamin D at two institutions without convincing benefit, and when she came to Cambridge she had been well pigmented from sunlight, natural and artificial. It was accordingly decided to treat the girl as a case of resistant rickets might have been treated and to give her very large doses of vitamin D. It was also decided to remove a small portion of bone from the upper end of the left humerus where the radiological appearances were highly abnormal, and to explore, and, if possible, to excise, the tumour from the lower third of the right femur. The operation was performed by Mr Fisk. A five-inch incision was made over the medial aspect of the leg over the swelling. The muscles were divided and the tumour exposed. The periosteum was found to be loosely attached. The tumour was pale and rubbery and could be cut like cheese. The edge was well defined. The whole tumour was enucleated, leaving about half the thickness of the femur, the cortex of which was very thin. The pathologist's report on this tumour will be considered later.

Vitamin D₂, 500,000 i.u. per diem in arachis oil, was prescribed on June 16, 1945, and no dramatic changes were detected in the first fortnight, but when the girl's calcium balance was redetermined from July 3 to 9, it was found that her output of calcium and phosphorus had fundamentally changed. The faecal calcium was now scarcely more than one-tenth of what it had been before, and, although her urinary calcium had risen, the total intake now greatly exceeded the output. These changes (Table II) are characteristically those produced by vitamin D, and it was evident that the outlook for the girl was now reasonably good. She began to go off her food about July 20 and it was thought that she might be suffering from an overdose of vitamin D,

so this treatment was discontinued on the 27th, by which time she had received 21 million units X-ray photographs taken in October 1945 (Plates 2, 3, and 4, Figs 1 c, 3 b, and 4 b) showed considerable recalcification and callus formation at the site of the pseudofractures (Edeiken and Schneeberg, 1943), and further balances in October and December 1945 and in March 1946 showed steady recalcification at the rate of about 5 gm of calcium weekly. The figures are given in Table II. By March 1946 the radiological appearances of many of the bones had become almost normal (Plates 2, 3, and 4, Figs 1 d, 3 c, and 4 c).

Apart from their value as a guide to treatment there are points of considerable interest about the balances shown in Table II. If in the first place

TABLE II
Results of Seven-day Balance Periods, 1945-6

Date		Total in	Out		Balance + or -
			Urine	Faeces	
June 3-9, 1945	Calcium	7,600	291	8,050	-741
	Magnesium	1,600	643	1,155	-198
	Phosphorus	8,860	4,950	3,950	-40
July 3-9, 1945	Calcium	6,660	1,110	842	+4,708
	Magnesium	1,500	785	620	+95
	Phosphorus	7,980	4,465	900	+2,615
October 13-19, 1945	Calcium	6,520	99	900	+5,521
	Magnesium	1,452	491	661	+300
	Phosphorus	7,540	3,750	506	+3,284
December 7-13, 1945	Calcium	8,000	144	1,130	+6,726
	Magnesium	1,430	420	616	+394
	Phosphorus	8,900	4,450	995	+3,455
March 20-26, 1946	Calcium	7,170	398	2,390	+4,382
	Magnesium	2,370	710	1,040	+620
	Phosphorus	9,160	4,650	1,720	+2,790

Tables I and II are compared, it will be seen that after May 1945 there was a rise in the inorganic phosphorus of the serum from 2.1 to 5.1 mg per 100 c.c. and that it remained above 4 mg per 100 c.c. for the rest of the year. Yet less phosphorus was excreted in the urine in July, October, and December than had been in May. This clearly indicates a change in the phosphate threshold of the kidney. This was presumably caused by the vitamin D (Harrison and Harrison, 1941), and suggests that Fanconi's disease might be treated successfully by large doses of vitamin D. In the second place treatment led to considerable retention not only of calcium and phosphorus, but also of magnesium. This is not altogether surprising, for most of the magnesium in the body is in the bones, but it is an interesting sidelight on the action of vitamin D. There is a third point. Treatment did not significantly alter the creatine/creatinine ratio in the urine. Hence the ratio was misleading as diagnostic evidence in the early stages of the disease, and it is interesting furthermore that it was not changed by the great recovery which subsequently took place in her muscular strength.

Symptomatic recovery accompanied the chemical and radiological improvements. In the summer of 1945 walking had been a very great effort to the patient, particularly in the early morning, and she had never felt safe on her feet. She could not stand alone to dress herself. By December she could walk with confidence, although she still required a crutch, and she was able to stand without support. Dressing had become easy and she could

bend down to pick things up from the floor. In July it had been a hard struggle for her to rise from a chair and she could do so only by employing her arms as well as her legs, and by exerting all her strength. So difficult, indeed, did she find the process of getting on to her feet that once standing, she dreaded having to sit down anywhere for a short time. She had to be lifted from her bath to a sitting position on the edge and then allow her legs to be swung over from the water to the mat. By December getting herself on to her feet had become a comparatively easy matter, and she thought little of it. She could get out of her bath without assistance, although she still found this rather a struggle. Best of all perhaps, by December she had lost all her pain. After seven years life had once more become pleasurable. Progress continued without interruption during the spring of 1946 and by June the girl was catching buses and looking for lodgings preparatory to finding herself some work. There is one more point of interest about the treatment of this patient. She weighed 7 st 6 lb on admission and in spite of the great clinical and radiological improvements which took place between May 1945 and the spring of 1946, her weight remained about the same.

Description by Dr A M Barrett of specimens of bone removed at operation
(Dep Path 45 404)

Macroscopic

Femur Four pieces which could be fitted together to form an irregular slice (17 cm \times up to 3 cm) from the shaft of the femur. The whole specimen was sufficiently flexible to be bent and the greater part consisted of a tumour-like mass (15 \times 3 \times 3 cm approximately) which had the consistency of cartilage and could easily be cut with the knife. Its uniformly white outer surface, bulging somewhat, but apparently covered by periosteum, was beset with many small nodular protruberances (0.1 to 0.2 cm in diameter). Towards one end (the lower end according to information sent with the specimen) the bulging ceased abruptly at a diagonal line below which the outer surface was smooth and even, like that of a normal femur, towards the other end the transition to normal was gradual. On the cut surface the mass was seen to encroach upon the medullary cavity more than it bulged beneath the periosteum. In the lower two-thirds its cut surface was greyish-white, smooth, and uniform, except for an ill-defined yellowish meshwork, gritty to the knife, about the middle, in the upper one-third it was greyer and more granular and showed channels apparently containing red marrow. The appearance of this upper part suggested that the mass might have arisen by the fusion of greatly thickened trabeculae. The borders of the mass, though fairly sharp, also showed evidence of a transition to bone. Even in the most normal part of the specimen the structure of the bone was decidedly abnormal. A corticalis was recognizable only at the upper end, and here it was excessively thin (about 0.1 cm). At the lower end, although the outer surface was relatively normal, the cut surface showed no corticalis, but only a spongy mass of rarefied cancellous bone. The marrow everywhere was mainly yellow, with here and there a little red, and in it were embedded rather coarse soft greyish trabeculae.

Humerus One small piece of bone (1.5 \times 0.6 \times 0.6 cm) having a concave periosteal surface overlying a thin corticalis (about 0.1 cm thick). The rest of the specimen consisted of dense cancellous bone with enlarged fused greyish trabeculae enclosing islands of red marrow.

Microscopic

Celloidin sections were prepared from material fixed in formol-saline and decalcified incompletely in Muller's fluid for about six months. These sections were stained by Delafield's haematoxylin and eosin, Schmorl's thionin-phosphotungstic acid, Schmorl's picro-thionin, von Kossa's method for calcium, and Macfarlane's picro-Mallory stain. Paraffin sections of material fixed in formal-saline or mercuric chloride-formaldehyde and decalcified by Custer's method were stained by Ehrlich's haematoxylin and eosin, Weigert's iron haematoxylin and van Gieson's stain, and Macfarlane's picro-Mallory stain.

Femur Sections of the tumour showed it to consist of close-set rounded and cylindrical hyaline masses separated by clefts of variable size. The hyaline masses stained uniformly pink with haematoxylin and eosin, but when stained by picro-Mallory they were deep blue and were seen to have a delicate fibrous structure. With van Gieson's stain they were orange-red. These hyaline masses mostly bore little resemblance to bone, but nevertheless every transition stage could be found between them and perfect lamellar bone. Scattered throughout the tumour there were areas (Plate 4, Fig 5, bottom left) which had the structure of lamellar bone but were not calcified, that is, they were osteoid. Some such areas were sharply outlined and these were usually devoid of nuclei, in others, usually surrounding blood-vessels, the lamination gradually faded and disappeared as the distance from the blood-vessel increased. In these latter areas bone-cells were usually present, though scanty and imperfectly formed. Except for very few small areas (Plate 4, Fig 5, below the centre) there was no calcification within the tumour, but the transition from osteoid to bone could be seen at its borders. The hyaline masses were invested by a layer of flattened, or occasionally almost cubical, cells reminiscent of osteoblasts. Some of the clefts between the hyaline masses were empty, others were filled with vascular, rather cellular, fibrous tissue often containing giant cells which closely resembled osteoclasts. The fibrous tissue resembled the fibrous marrow seen in rickets and various other bone disorders. Taking everything into consideration, I am convinced that the tumour consisted of degenerate osteoid tissue and was not truly neoplastic. The bone of the femur apart from the tumour showed a great excess of uncalcified osteoid tissue which was irregularly distributed. Some trabeculae were completely devoid of calcification and others were partly calcified, but it was not merely a question of abnormally wide osteoid seams surrounding cores of calcified bone, the margins of the calcified areas paid no regard to the laminations of the bone, often cutting across them at right angles. The flattened appearance of the osteoblasts around the borders of the trabeculae suggested that apposition was at most only moderately active, osteoclasts in Howship's lacunae were present but infrequent, and the trabeculae were embedded in marrow which was a mixture of fat and normal haemopoietic tissue.

Humerus As in the femur, osteoid tissue was present in greatly excessive amounts (Plate 4, Fig 6). Both apposition and resorption appeared rather more active than in the femur, some trabeculae were surrounded by large irregularly-cubical osteoblasts and others were being attacked by numerous osteoclasts. The corticalls proper (Plate 4, Fig 6, right) was abnormally narrow, but was nowhere interrupted, and the tissue underlying it was much more compact than usual, constituting in effect an accessory corticalls, though its rigidity must have been much impaired by the large amounts of osteoid which it contained. One area (Plate 4, Fig 6, top right) had an

appearance very like that of normal callus and was well calcified. This may have been a result of the vitamin treatment which was begun before the specimens were obtained.

Conclusions

The histological changes are those of osteomalacia, with a tumour-like mass of degenerate osteoid tissue in the femur. Excess of osteoid tissue is a constant feature of osteomalacia, but I think that tumour-like masses such as this are exceptional.

Discussion

The diagnosis When Milkman (1934) published his case of multiple spontaneous idiopathic symmetrical fractures he considered that he was dealing with an undescribed condition of unknown but specific aetiology. In the first sense he was wrong, for Looser (1920*a, b*) and others had reported on the bony appearances long before, and Milkman knew this. In the second sense he appears also to have been wrong, for it now seems clear that the symmetrical bands of decalcification are not a feature of any one disease, but are likely to be met with whenever the skeleton has become sufficiently decalcified (Camp and McCullough, 1941, Lافitte and Gros, 1942). They are in fact one of the signs of gross decalcification. Whatever the metabolic abnormality which produces the appearances of pseudofractures, it should clearly be regarded as a localized intensification of a generalized process rather than a disease *sui generis*. In believing that the absence of callus formation was a characteristic feature of his syndrome Milkman would also appear to have been in error. Absence of callus merely indicates complete absence of healing at the time the photograph is taken. The essential features of the present case seem to be perfect health before puberty, a progressive illness characterized by pain, weakness, decalcification and skeletal deformity, and cure of the metabolic abnormality by very large doses of vitamin D. There is no suggestion of any renal, intestinal, or dietetic reason for the decalcification, which did not respond, moreover, to normal therapeutic doses of vitamin D. The logical conclusion, therefore, seems to be that this patient was suffering from something which prevented normal supplies of vitamin D from exerting their usual effects. It is suggested that this was a raised resistance to vitamin D (*vide infra*) which she acquired about the age of puberty. It is further suggested that this disease entity be termed 'raised resistance to vitamin D', or more briefly R R D, and that, since her metabolism in early life was normal, it should further be designated by the word 'acquired'. A congenital form will be described later.

The disease Acquired R R D is not a new disease, for a syndrome which must be regarded as clinically identical in its onset and development has certainly been described before. It is, however, new in the sense that the disorder has never been conclusively cured by vitamin D and hence that its true nature has never been established and appreciated. The novelty lies in the diagnosis rather than anything else, as the following records show.

Debray, Thomann, and Gireaux described a case in 1933 which in many ways resembled the present one. A woman of 51 years with a negative Wassermann reaction had suffered for over 10 years from pain and muscular weakness, and when seen her bones were found to be in a state of advanced decalcification with pseudofractures. She had borne and nursed four children and her rheumatic-like pains had begun soon after the birth of her last child. For these symptoms she had been sent into the country for some months and had returned apparently cured, but she had relapsed in Paris. She had been sent again for treatment to the country, only to relapse once more on her return. She had deteriorated considerably in the three or four years before admission. Her serum-calcium was 11 mg per 100 cc and serum-phosphorus 2.4 mg per 100 cc. Some further biochemical investigations were carried out, but she refused to allow her parathyroids to be explored, and ultimately was discharged after being treated with arsenical drugs, but seemingly no vitamin D. Six months later she was readmitted considerably improved both clinically and radiologically. She had gained 2 kg and in the following months gained more weight and recovered a great part of her strength. No diagnosis was made.

Milkman's (1934) case was that of a woman aged 43 years who had been fit and well till 1925. In that year, when she was 34 years old, she began to have pain on movement and weakness, but no radiological abnormalities were detected at that time. Her condition steadily deteriorated, however, and in 1928 a diagnosis of osteomalacia was made. Her basal metabolic rate was +5 per cent of normal. Aspirin apparently gave most relief and there were no remissions in spite of a variety of treatments, some of which were phosphorized cod liver oil, sunlight, and viosterol, and in 1931 the woman developed diabetes and became completely bedridden. She died two years later.

Leedham-Green and Golding (1937) recorded a case of some interest. A woman, aged 24 years, who had had a good diet all her life and who had never been pregnant, had been suffering for six years from a disabling and painful affliction. This must have been relatively mild for she was not completely incapacitated by it. She had had at least three remissions. The first followed a course of treatment with iron, the second one with iron and liver, and the third one with ultraviolet light and marmite. Her serum-calcium was 9.6 mg per 100 cc and plasma-phosphorus 2.2 to 2.8 mg per 100 cc. X-rays showed extensive decalcification of the skeleton with Looser's nodes. The authors treated the patient with radiostoleum, but, knowing that Milkman's case had shown no response to similar treatment, they did not really expect to cure their patient and presumably did not do so.

One of the few men who seem to have suffered from this syndrome was described by Michaëlis (1932). This patient's trouble began in 1917 when he was serving, as a young soldier of 18 years, on the Eastern front. Owing to the socio-economic state of Germany, Michaëlis seriously considered malnutrition as the underlying cause of his patient's condition, but there is no

reason to suppose that this man was undernourished in 1932, for he had spent the greater part of his illness in one hospital or another, and various diagnoses from osteomalacia to hysteria had been entertained from time to time. He had changed little for better or worse between 1926 and 1932. His serum-calcium was 11.6 to 12.6 mg per 100 c.c. and his inorganic phosphorus 1.6 mg per 100 c.c. He had bilateral coxa vara and decalcification of his bones with pseudofractures.

A peasant girl, brought up in healthy surroundings and on country food, first began to find muscular effort painful and difficult when she was 18 years of age (Momer-Vinard, 1940). She became steadily worse for the next six years, and lost 12 kg. in weight. Her X-ray appearances were characteristic, but she differed from the case described in the present paper and most of the other cases in having a low serum-calcium and severe tetany. This may be merely an expression of the fact that her parathyroids had failed to hypertrophy sufficiently to maintain her serum-calcium within normal limits. She was treated for 10 weeks with a good diet, injections of calcium gluconate, vitamin D, ultraviolet light, and parathyroid extract. She improved sufficiently to make her own way up and down stairs and she gained some weight, but no firm diagnosis was made.

Garcin, Legrand, and Bernard (1937) described a case of Milkman's syndrome in a nun aged 58 years, who gave a six-months' history of trouble in walking. Her initial symptom had been difficulty in rising from her knees after prayer. The diet in a religious house may not have been all that it should have been and this woman may have had very little exposure to sunlight, but no other inmates seem to have been similarly affected. This was, therefore, probably a case of acquired R.R.D. The patient responded well to vitamin therapy over a period of 10 months, but unfortunately the dosage was not recorded.

Roger and Huguet (1938) described a woman aged 62 years, probably well to do, who had suffered for six years from pain on movement, and had become progressively worse for the previous three years. Her bones showed decalcification with Looser's nodes, and she was treated with deep X-rays, calcium, irradiated ergosterol, phosphates, liver extract, and snake venom. She recovered slowly, and in four years was free from pain.

A case was described by Edeiken and Schneeberg in 1943. Their patient was a woman aged 34 years who had probably had osteomyelitis at the ages of seven, 14, and 30 years, and had certainly had bony diseases of one or more kinds for most of her life. She is stated to have had a remission at 26 years. At 30 years she was found to have generalized decalcification of the skeleton and some fractures, and at 34 years the diagnosis of Milkman's syndrome was made. A footnote to the paper shows that this was almost certainly a case of acquired R.R.D., for after the administration of 50,000 U.S.P. units of vitamin D daily for 25 weeks she is said to have gained 8.6 kg., to have lost her pain, and to have shown radiological signs of recovery. It is curious that the authors should have continued to regard the disease they were

investigating as one of unknown aetiology. They evidently did so, however, for their summary contains the words 'The aetiology and pathogenesis are unknown. Several reported cures have resulted from treatment with calcium, vitamin D, arsenicals and vitamin A.' This case is so complicated by the recurrent osteomyelitis that it is impossible to say when the R R D began. It was probably not till after puberty, for had it been before, one would have expected signs of late rickets to have been discovered when she was under observation as a child.

The relationship between resistant rickets and acquired R R D. Resistant rickets is now a well-known if uncommon disease which may affect several members of the same family. The disease was first cured by Albright, Butler, and Bloomberg (1937) who first gave the very large doses of vitamin D now recognized to be necessary. The majority of the cases which have been reported have been reviewed by Lussy (1946), and Mackay and May (1945) have added two more to the literature. Some of these children have undoubtedly been affected from birth (Bornscheuer, 1931; Liebe, 1939; Mackay and May, 1945), and the bargee's child described by Halbertsma (1935) must also be reckoned in this category. These cases might be styled congenital R R D. A child of this type has been under observation in Cambridge for years. Others have appeared to be normal children till they were one, four, seven, or even more years of age. Beumer (1943), for instance, described the development in a month or two of resistant rickets in a child aged four years 'früher immer gesund'. There was nothing to suggest that the boy described by Albright, Butler, and Bloomberg (1937) was in any way abnormal till he was over one year, and Nadrai's (1938) patient is stated positively to have developed normally till she was 18 months old. In Highman and Hamilton's (1936) case the disease may not have begun till the child was two years of age, and Bakwin, Bodansky, and Schorr's (1940) boy seems to have had a normal calcium metabolism till he was six years old. A case of great interest in the present connexion was described by Linder and Vadas (1931). Their patient was a coloured errand-boy in Cape Town and seems to have been perfectly well till he was 15 years old. At that age he was given a short course of antisyphilitic treatment for vague pains in the shins. The diagnosis was doubtful, but the treatment was successful and the pains vanished (compare the woman described by Debray, Thomann, and Gireaux, 1933). Two years later he began to have pain in his knees and from that time onwards became more and more incapacitated, and unable to earn any money. After a period of semi-starvation he was admitted to hospital. There he was found to have the waddling gait of a muscular dystrophy, a serum-calcium of 12.6 to 14.0 mg per 100 c.c., an inorganic phosphorus of only 1.2 mg per 100 c.c., epiphyseal changes, and gross skeletal disorganization. His parathyroids were explored and a small adenoma was found, but its removal made no permanent difference to his calcium metabolism. He was under observation for two years and was treated, at any rate for a time, with 18,000 i.u. of vitamin D daily, but without any real improvement. The case was described as one of late rickets, and the authors commented on the low renal threshold for phosphates.

It is evident that this was a case of acquired R R D, very like the present one in some respects, and particularly in the age of onset. In all these children, therefore, the correct diagnosis seems to be acquired R R D. Whether the bony lesions receive the label rickets or osteomalacia is probably only a matter of the age at which the resistance developed. Mackay and May (1945) made another point of some interest. They pointed out that the resistance of some of these children to vitamin D varied very much from time to time. It will be recalled that remissions have been a feature of the disease as seen in later life. In children it has been shown (Bakwin, Bodansky, and Schorr, 1940) that enormous concentrations of the vitamin have to be present in the serum and body fluids to effect a cure. Hence in them certainly, and in adults probably, the metabolic fault is a true internal resistance and not a failure of absorption.

Resistance to vitamin D. It is well known from the cases of resistant rickets which have been recorded that the amounts of vitamin necessary to effect a cure or maintain health differ very much from one patient to another. They also differ in the same patient from one time to another. It is probable that every grade of resistance exists between the 'normal' and the most severe, and the same is certainly true of acquired R R D in adults. This statement implies that even in normal persons there must be some factor or factors which resist the action of vitamin D. There is, moreover, evidence that this is so, for McCance and Widdowson (1943) have shown that the season of the year affects the response of normal persons to vitamin D. It is possible that species differences in vitamin D requirements, that is, between the rat and man, may be explained in terms of vitamin D resistance, but this is mere conjecture. The nature of the metabolic processes involved in vitamin D resistance is quite unknown. Suggestions ranging from focal infection to psychological trauma have been considered. It is possible that in some instances the thyroid hormone plays some part, for rarefaction of the bones is a well-recognized feature of thyrotoxicosis, and in this connexion it may be mentioned that the woman described by Guillaumin, Lereboullet, and Auzépy (1937) as a case of Milkman's syndrome, and who may have been an acquired R R D, had a basal metabolic rate 41 per cent over the normal. There is, however, no suggestion that all cases of acquired R R D have thyrotoxicosis. The majority have not.

It may seem to some that to say that resistance to vitamin D may vary from one person to another is merely another way of stating that no two individuals' requirements are the same, and that it would be better to use the latter and more familiar term. It is true that if resistance is high requirements are also high, but children who are not known at present to have higher resistance than adults have certainly got higher requirements. Variations in resistance, moreover, have been detected in adults (McCance and Widdowson, 1943) whose requirements could not be measured, and finally persons with very high resistance may require so much vitamin D to overcome it that they suffer from toxic effects of the vitamin (Mackay and May, 1945, personal experiences). To apply the term requirement to therapy at this level of dosage is to use the word in a very unusual and rather misleading sense.

Summary

1 A girl who had been in perfect health till she was 14 years old developed osteomalacia (with Milkman's syndrome) during the next three years of her life. Her kidneys and intestinal tract were normal, and her diet was good.

2 The patient was cured by large doses of vitamin D and it is, therefore, suggested that her illness was due to a raised resistance to vitamin D, acquired about the age of puberty.

3 Perusal of the literature shows that acquired 'raised resistance to vitamin D' is an uncommon but well-recognized disease of childhood, generally at present referred to as resistant rickets, and that a syndrome clinically resembling it has been described in adults.

4 The disease affects children of both sexes, but mostly women in later life. It produces rachitic changes in children, and progressive weakness, pain, and decalcification of the skeleton in adult life.

5 The disease must be distinguished from 'chronic rheumatism', generalized osteitis fibrosa, and osteoporosis of the spine. It is unlikely to be confused with other disorders of metabolism.

6 During the course of treatment vitamin D was observed to raise the renal threshold for phosphate and to promote retention of magnesium.

I am indebted to a number of persons for helping me with this investigation. Dr J. H. Sheldon first introduced me to the patient and the late Dr Izod Bennett kindly allowed me to study her and to publish the results. Dr Nevin provided me with X-rays taken in 1939 and Dr Dean took part in the clinical work at Addenbrooke's Hospital. The mineral balance determinations and many other points of detail were entirely the work of Miss Thrussell.

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FIG 1 a Pseudofracture on the left side of the pelvic brim



FIG 1 b Separation of the pubic bones, multiple spontaneous pseudofractures in the pelvis and femur Thinning of the cortex of the shaft of the femur

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FIG 1 *c* Callus formation at the site of the pseudofractures, particularly in the pubic bones



FIG 1 *d* The healing of the pseudofractures is almost complete. The deformities persist

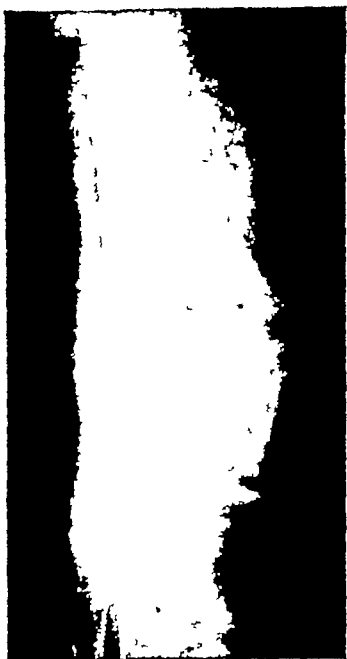


FIG 2 Large defect in the medial side of the lower third of the right femur Pseudofracture in the tibia



FIG 3a Symmetrical pseudofractures in the R and L ulnar bones



FIG 3b Callus formation at the site of the pseudofracture in the R ulna



FIG 3c Dense callus and consolidation of the pseudofracture in the R ulna

OEDEMA IN AN INTERNMENT CAMP¹

By R. A. PALLISTER

AN account is given here of the types of oedema observed in the male civil internment camp in Singapore during the period that Malaya was occupied by the Japanese. As the staple article of diet of the internees was rice, and this usually of the polished variety, one of the main dangers to health appeared to be beriberi. It will be shown, however, that among the many cases of oedema observed, those due to beriberi were not numerous and were confined to a period when the estimated value of vitamin B₁ in the food was low. As only a small stock of aneurin was available for treatment during most of the period of internment, it had to be reserved for beriberi only, and the differential diagnosis of a patient who had developed oedema was of great importance. The diagnosis of beriberi is still dependent on clinical observation, and the different manifestations of the disease have at times led to difficulties. Nearly fifty years ago Manson (1901), in speaking of beriberi, found it necessary in order to avoid confusion to describe what he meant by this diagnosis. Although we now have the therapeutic test with aneurin this explanation is still desirable to-day. A fairly complete account is therefore given of those cases that appeared to be beriberi as well as those where the oedema was considered to be from a different cause, and the diagnoses are discussed. The cases are divided into three series. In the first are included those who probably had beriberi, and the second and third consist of cases of nutritional oedema from other causes. The last two series appeared to be different from each other, but little definite can be said of their aetiology.

The period of internment lasted from the middle of February 1942 to September 1945. The population was mainly European and varied from 2,360 at the beginning to 3,175 in the last year. A detailed account of the diet will not be given here, but the main particulars relevant to the paper are shown in Figs 1 and 2. It will be noted that in the first three months of internment the amount of vitamin B₁ in the diet was very low. The food at this time consisted of polished rice supplemented by tinned provisions, and was defective in many respects. For the rest of the period of internment vitamin B₁ never fell below about 250 international units per diem, which would be generally accepted as well above the beriberi danger-level. The total calories and the protein were low for most of the time and fell to a dangerous level in the last few months. The high figures for protein in the first quarter of 1944 were the result of a supply of soya bean. Most

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oedema was mild and usually only around the feet, ankles, and shins. In two cases there was swelling to above the knees, and two patients had a little puffiness of the face in the mornings. Four complained of a tense or tight feeling in the calf muscles, and three or four others were also noted to have a fullness in the calves. Even with the leg hanging loosely the muscles

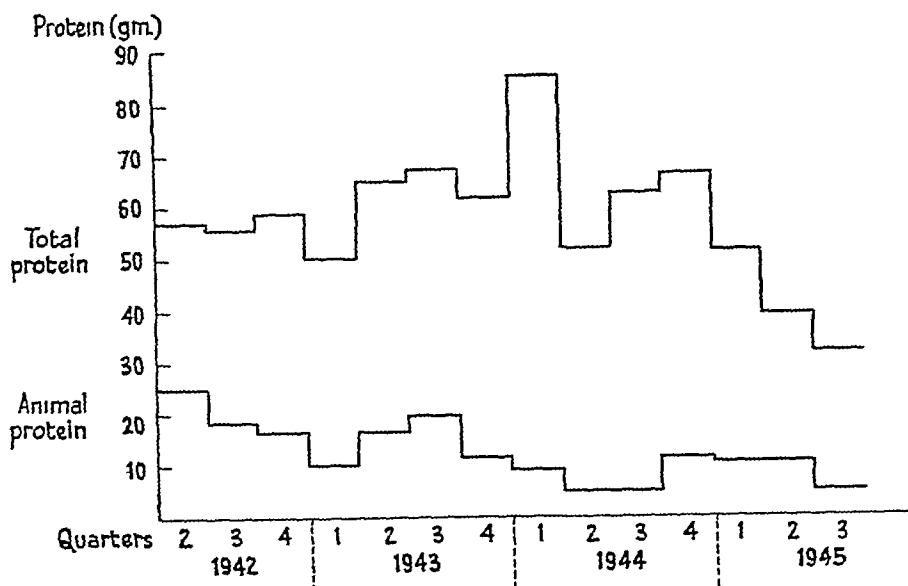


FIG 2 The average daily total protein and animal protein

felt firmer than normal and a little swollen. Slight tenderness was noted in two, and two complained of some pain. Mild tingling or paraesthesia was mentioned by four patients. Two had definite weakness of the legs. These were mixed types and the remaining 14 were essentially cardiac. Breathlessness was complained of by seven patients, and one of these also said that he felt tired. One or two others, however, were obviously dyspnoeic on exercise. Two had some chest discomfort and two said that they had some loss of appetite. Most of them had a moderate tachycardia of from 80 to 110 per minute. These readings were taken with the patient lying down. When standing, readings were about 15 beats higher. The pulse was usually full, and low diastolic pressures with a high pulse-pressure when first examined were noted in two cases. The readings of these two patients (Cases 6 and 9) are given in Table II. The changes in the heart varied from no obvious abnormality up to the typical pictures of acute cardiac beriberi with venous fullness in the neck, wavy praecordial pulsation, increased cardiac dullness, systolic murmurs, and accentuated or reduplicated pulmonary second sounds. The knee reflexes and ankle reflexes were absent in six patients. The ankle reflexes were absent in eight, and two of these patients lost their knee reflexes while under treatment. Two patients retained the knee and ankle reflexes. All the patients were treated with

internees were unable to take their full share of this food as it led to indigestion and diarrhoea. The amount of protein actually available at this time was therefore much lower than Fig 2 shows. The foodstuffs that supplemented the basic rice ration varied at different times, but probably the leaf vegetables that were supplied in increasing quantities from the camp

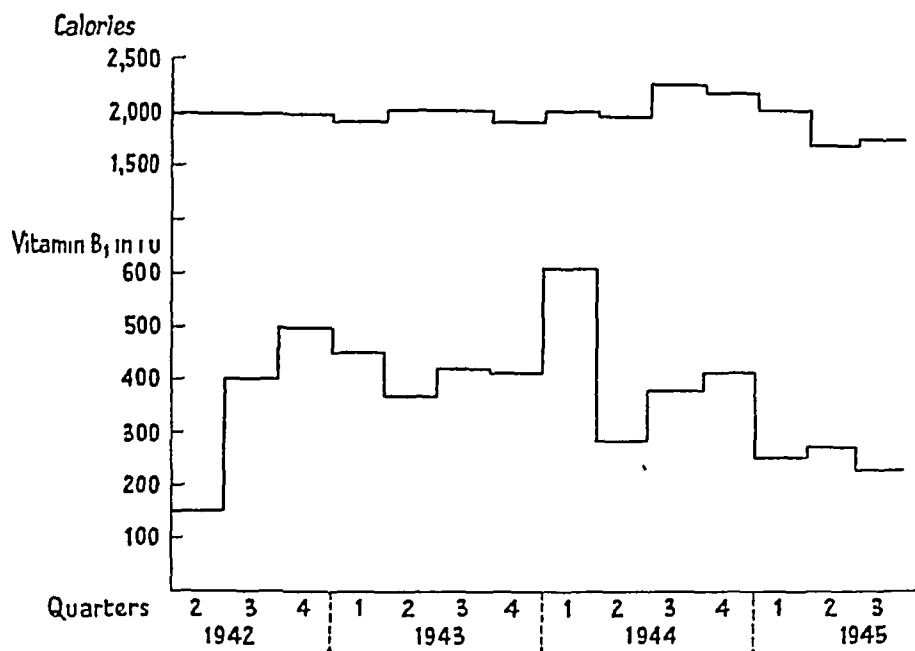


FIG 1 The average daily calories and vitamin B₁ shown in three monthly periods. The values for B₁ are expressed in international units. Figs 1 and 2 are based on 'workers' diets. Those unable to work received less food in the latter months.

gardens after the first few months provided the most useful source of minerals and other accessory food substances.

Series 1 A mild epidemic of beriberi started after about three months' internment and ceased two months later as a result of an all-round improvement of diet, which included rice polishings. There were about 20 cases. Of

TABLE I
Ages of Beriberi Patients

20 to 29 years	3
30 " 39 "	2
40 " 49 "	4
50 " 59 "	5
60 " 69 "	2

(The average age of the internees was 43 years.)

these one had mainly peripheral neuritis and the remainder were mixed or mainly cardiac in type. Fairly good records are available of 16 of the latter group. The age groups are given in Table I. The monthly incidence is shown in Table III. All the patients had oedema as one of their complaints. The

pulmonary congestion or cardiac asthma. In one (Case 3) there was nocturnal cough and some wheezing, dating from just before the beginning of treatment, but worst on the first four nights after aneurin had been given. The other (Case 4) was awakened on the second night after treatment was started with a feeling of breathlessness. It was not sufficiently severe for him to call for the doctor. One other patient (Case 1), the most dangerously ill of all, had a severe attack of cardiac asthma on the first night after aneurin was started. He became greatly distressed with dyspnoea and cough. The pulse-rate was rapid, the veins in the neck distended, and he was cyanotic. He was restless and could not decide whether it was more comfortable to sit up or lie down. This attack did not come on until six or seven hours after he had had an injection of 12 mg of aneurin. He was given more aneurin and 30 oz of blood were drawn off with some relief. He was given morphia on subsequent nights and the attack was not repeated. The blood-pressure in his case showed no very significant change except that the diastolic level was low. He also suffered from an aneurysm of the subclavian artery. He made a good recovery and was soon quite active again and remained well for about two years. There can be little doubt that his illness was due to beriberi, but an unhealthy heart played a part in the severity of his attack. Records are available of the temperatures of eight of these patients while under treatment. Case 1 had a temperature of 99.2° F on the second day, Case 3 101.2° on the second day, Case 4 100.2° on the fourth day, and Case 5 99.4° on the second day. Cases 2, 6, 9, and 11 were below 99° F. It will be noted that three of the patients, namely, Cases 1, 3, and 4, who had some fever were those recorded as having probably some pulmonary congestion.

This completes the account of the outbreak of beriberi that occurred in the early days of the camp when the general state of nutrition still remained fairly good. After this time there were no other definite cases of beriberi among those residing in the camp. There were, however, a number of men removed by the Japanese military police for special questioning among whom beriberi occurred. These men were subject to some violence and were imprisoned in very unhygienic conditions of overcrowding and underfeeding. At different times and usually after many months they were returned to the camp either because the questioning was finished or the state of health so dangerous that death seemed likely. Among these were two (Cases 17 and 18) who seemed definitely to be suffering from beriberi among their many troubles and three others (Cases 19, 20, and 21) who are included here as cases of beriberi, though certain features place them in a separate group and merit some discussion. These five cases are not included in the previous analyses.

Case 17 (Aged 49 years) This man had been in the custody of the military police for some months. He complained of complete exhaustion and loose stools for about four and a half months. He could barely move in bed. He had severe oedema affecting the dependent parts and, where not

aneurin and all recovered Dosage varied from 36 mg by injection on the first day for the most dangerously ill patient down to 4 mg for mild cases The subsequent doses were low The reactions of the cardiovascular system during recovery are worth recording Cases 6 and 9, who showed the lowest diastolic blood-pressure readings on admission, were both young men The diastolic pressure showed a rapid rise accompanied by slowing of the pulse and they made uneventful recoveries The readings are shown in Table II Four of the other patients who had blood-pressures within normal limits when first seen showed a rise in systolic and diastolic pressures with slowing of the pulse-rate after treatment with aneurin Details are given in Table II Of these patients two (Cases 3 and 4) had some symptoms of possible

TABLE II

Case 6 (Aged 23 years)

Day	1	2	3	4	17	38
Blood-pressure						
Systolic	118	112	125	120	135	125
Diastolic	40	70	80	70	85	70
Pulse rate	80	58	60	56	—	—

Case 9 (Aged 28 years)

Day	1	2	3	4
Blood-pressure				
Systolic	135	130	125	130
Diastolic	40	80	65	70
Pulse rate	84	60	60	48

Case 3 (Aged 52 years)

Day	1	7	19
Blood-pressure			
Systolic	142	160	130
Diastolic	85	95	90
Pulse rate	110	64	84

Case 4 (Aged 46 years)

Day	1	2	3	4	5	7
Blood-pressure						
Systolic	110	135	145	160	130	115
Diastolic	70	85	85	90	80	70
Pulse rate	96	—	60	52	60	64

Case 11 (Aged 47 years)

Day	1	2	3	4	6
Blood-pressure					
Systolic	115	115	158	125	125
Diastolic	65	70	100	70	70
Pulse-rate	100	68	68	50	60

Case 16 (Aged 66 years)

Day	1	4	9	23
Blood pressure				
Systolic	170	180	200	180
Diastolic	90	90	100	100

(This patient also suffered from mild hypertension)

contained pus cells, macrophages, and red cells. The urine was scanty, dark in colour, and contained albumin and a few cells. A blood examination was made at a later date and compared quite well with the rest of the camp. The red-cell count was 3,880,000 per c mm and the haemoglobin 78 per cent. Aneurin injections were given as shown in the table, and aneurin, ascorbic acid, and vitamin A were also given by mouth. The blood-pressure readings are also shown in the table.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Blood-pressure													
Systolic	115	160	160	160	160	160	160	—	160	160	155	150	150
Diastolic	70	95	95	90	100	100	100	—	100	110	100	100	100
Vitamin B ₁ (mg)													
by injection	15	10	5	5	5	5		5					

The flow of urine was noted to be better after 48 hours, and an examination on the seventh day showed the urine to be free from albumin. At this time it was thought that the oedema was beginning to go down, but on the night of the ninth day and for the following two days there was a large diuresis with a loss of oedema. On the fourteenth day the oedema had gone and the patient was seen to be extremely emaciated. On the morning of the tenth day, after telling of his diuresis, he complained of being troubled by cough during the night, and on examination of the chest a few basal crepitations were found. On this day and for a few days after, his evening temperature was between 99° and 100° F. Unfortunately earlier temperature records are missing. It will be noted that the most marked diuresis coincided with the highest blood-pressure reading and was accompanied by nocturnal cough and slight fever. After three weeks in hospital the skin was clear and the bowels practically normal. His feet felt numb and there was blunting of sensation to pin-prick over the legs and arms. The heart seemed slightly enlarged and the rate was increased to 80 to 90 at rest. The sounds were less 'tic-tac', but there was a 'slapping' quality about them. The blood-pressure was still 150/100. Sitting up in bed was possible for a short time only and caused considerable tachycardia. After six weeks he was feeling very well and putting on weight. He was still unable to leave his bed and the exercise tolerance only a little improved. There was still a moderate tachycardia and the blood-pressure was the same. He was removed from the camp and not examined again. The case is recorded because of the peculiar nature of the oedema and also to show the response to treatment.

Case 19 (Aged 43 years) This patient had been nearly one year in the custody of the Japanese military police and he was brought back to the camp after a tedious journey in an open lorry during which he had been soaked with rain. He complained of oedema which had started about three weeks previously and had been very severe for one week. There had been some fever a week before the oedema started. He had been able to walk until he became oedematous. The bowels had been loose for about eight months. On examination he had a temperature of 100° F. There was severe general anasarca. Unlike the last patient, the scrotum was very swollen. A little of the oedema was of the 'jelly' type previously mentioned. He had sores on the hands and feet from scabies. The tongue was clean and the appetite good. The heart-sounds were fairly good and there were no murmurs. The blood-pressure was 168/90 and the pulse-rate 82. The tendon reflexes were all brisk and the calves were not tender. There was no cellular exudate in the stools. He was mentally bright and cheerful. He

oedematous, was seen to be very emaciated. The heart sounds had a 'tic-tac' rhythm and the pulse was 110. The tendon reflexes were all absent and there was slight tenderness of the calves. There were pus cells and red cells in the stools. He was given 8 mg of aneurin intravenously on the first day, and 4 mg intramuscularly on the second, followed by 3 mg a day by mouth. Some of his blood-pressure readings while he was in hospital are given below —

Day	1	2	10	20	25	26	27	28	42	71	76
Blood-pressure											
Systolic	115	110	140	145	130	130	140	110	130	150	130
Diastolic	80	72	90	90	100	100	100	90	100	105	90

He had a little fever with a maximum temperature of 101.2° F between the sixth and ninth days. There was, however, little change in his condition at first, but he began to pass urine more freely before the twentieth day. He was taking some potassium citrate and this may have contributed to the diuresis. It was, however, during the next week or 10 days that he had a real diuresis with loss of oedema. On the 24th night he had a gripping feeling in the chest and the following two nights had attacks of breathlessness. Morphia was given for this on the second night. From the blood-pressure readings it was noticed that these symptoms were associated with a slight rise in pressure. The second rise in pressure was not associated with symptoms. The heart-rate was a little rapid the whole time. He ultimately made a fairly good recovery and was able to leave hospital in about four months. His legs were still weak and he could not rise from the squatting position. The knee and ankle reflexes were absent and his blood-pressure was 110/85.

Case 18 (Aged 44 years) This patient was admitted to the camp hospital on his return from the military police with general anasarca, breathlessness on exertion, and diarrhoea. He stated that about six months previously he had developed oedema and scabies for which he had been given treatment in hospital with some benefit. Two months later he had swelling again and dysentery. The swelling improved, but the bowels remained irregular. A month before admission to the camp hospital the present swelling came on.

On examination he was mentally bright and cheerful. He lay flat in bed and the slightest exertion caused breathlessness. He had severe general anasarca. His face, trunk, and limbs were all very swollen, but the scrotum was spared. The absence of oedema of the scrotum is occasionally found in wet beriberi according to de Langen and Lichtenstein (1936). Over the front, that is the uppermost part of the body, the swelling was of a peculiar jelly-like consistency that did not pit on pressure. In the dependent parts there was also pitting oedema of the common type. He had scabies of the hands and feet. The tongue was tremulous and rather red and there were cracks at the corners of the lips. There was dermatitis of the scrotum. The calves were tender and he had some general muscular pains. The knee reflexes were absent. Examination of the heart was made difficult by the oedema, but no enlargement was demonstrated. The veins were full in the neck, but the patient was lying flat. There was some epigastric pulsation. The heart sounds were clear but with a marked 'tic-tac' rhythm. At the base the first sound was poor and the second rather loud. The pulse was full and the rate 114. The blood-pressure was 115/70. The abdomen was distended and tender. The liver could not be palpated. The faeces

day and was ordered vitamins by mouth. He passed urine fairly well during the first four days. He developed a headache and on the sixth day had wheezing on breathing. The blood-pressure was then 160/100 and the pleural cavities showed evidence of effusions. On the following day a little after midnight he had an attack of breathlessness, and treatment with morphia and digitalis was started. After this he gradually improved, and after a mersalyl injection on the eleventh day he passed 10 pints of urine. During the worst four days of his illness he had some fever and the pulse-rate was up to 110. After this time the pulse-rate was between 50 and 60. The convalescence was slow and he had some nocturnal wheeziness and occasional headaches during the first month, though the oedema was only slight after the first two weeks. He left hospital after three and a half months and was under observation for a further four months. The tendon reflexes remained brisk the whole time and the blood-pressure, though it varied a little, was usually about 160/90.

Discussion. The first group of 16 cases which comprised the small beriberi outbreak in the camp and the following two from special military custody were all cases of fairly typical beriberi. The blood-pressure changes that occur during the disease and its treatment have been emphasized, and also the probability that with the onset of increased vascular tone resulting from the aneurin a strain is thrown on the left ventricle with the possible onset of cardiac asthma. Hawes (1937) and Hawes, Monteiro, and Smith (1937), in their early work in Malaya on the use of the pure vitamin in the treatment of acute cardiac beriberi, noted the blood-pressure changes, and they also pointed out that where diuresis cannot be established the blood-urea rises and death may occur in pseudo-uraemia. Weiss and Wilkins (1937) in the United States also observed the rise in blood-pressure after administration of the vitamin and they also noted lung signs that they considered might have been due to increased pulmonary congestion resulting from compensation of the right ventricle out of proportion to the left. If the two young men, Cases 6 and 9 in the present paper, who had typically low diastolic pressures when first seen had been untreated, they would probably have died with a pure right-sided heart failure and a dry lung like the cases described by Wenckebach (1928) in Java. On the other hand, some of the other cases I have described had during treatment, and Case 3 probably before treatment, some pulmonary engorgement and left-sided heart failure such as Weiss and Wilkins (1937) observed among their patients. The fever that was noted in some of the patients seemed to accompany congestion of the lungs and must be looked upon as secondary to the beriberi state. Infection as a factor in the aetiology of beriberi has been described by some writers, particularly Bernard (1931), but the evidence here does not support this view.

The last three patients described presented a rather different picture. The presence of brisk tendon reflexes in two of them was against the diagnosis of beriberi. The examination of the cardiovascular system gave little support to this diagnosis as the blood-pressure tended to be slightly

received injections of aneurin as follows from the first to the sixth day—8 mg, 4 mg, 0 mg, 10 mg, 28 mg, and 40 mg. In addition he received 3 mg daily by mouth and also ascorbic acid. He continued to have fever, but was fairly comfortable until the evening of the third day, when he had slight cough and did not seem so well. On the fifth day the oedema seemed worse and the urine was reduced in quantity. The heart was rapid and the blood-pressure 170/120. The knee and ankle reflexes were present. Mersalyl was given, but on the same night he had an attack of acute pulmonary oedema. On the eighth day he became comatose with hissing respiration. The urine was dark in colour and scanty. It contained albumin and casts for the first time. He vomited some black watery matter and the stools were tarry. He died in the early morning of the ninth day.

Case 20. (Aged 43 years) This patient was brought to camp with the last patient. He complained of oedema for five weeks. He also said that he had a little difficulty in breathing which he put down to the oedema. He had had diarrhoea, but the bowels had been normal for the past two months. He was bright and cheerful and the appetite was good. He did not seem distressed and there was no dyspnoea. He had severe general anasarca. In the anterior axillary folds this was rather of the 'jelly' type. There was some dermatitis of the scrotum. The temperature was 97.4°F. The tongue was clean and nothing abnormal was noted in the heart. The blood-pressure was 140/90 and the pulse-rate 78. On examining the lungs there was some dullness at the right base with bronchial breath sounds. The knee reflexes were not obtained, but the ankle reflexes were present though weak. With severe oedema the reflexes are not easy to see. The arm tendon reflexes were present except the right triceps. There was slight tenderness of the calves. Sensation was normal. He was given aneurin by injection in the following doses from the first to the sixth day—8 mg, 0 mg, 5 mg, 5 mg, 5 mg, and 6 mg. He also had aneurin and ascorbic acid by mouth. On the third day the knee and ankle reflexes could not be elicited and on this day he began to get an evening rise of temperature. Urine was passed in about normal quantities, but there was no change in the oedema. On the fourth day the blood-pressure was 130/75, but by the eighth day was up again to 150/90. Fluid increased in the pleural cavities and some was drawn off on the fifth, ninth, and tenth days. During all this time he was bright and apparently well except for the anasarca. He had some tightness in the chest, eased by removal of pleural fluid. On the night of the eighth day he was rather breathless. On the tenth day he seemed much the same, but after an afternoon doze he awakened with breathlessness and died in half an hour from acute pulmonary oedema.

Case 21 (Aged 52 years) This patient returned to the camp about one week after the previous two cases. He complained of oedema for some weeks and this had been severe for 11 days. There was some tightness in the chest and he had been breathless on exertion for two days. For five days before admission he had passed very little urine, but this had improved on the last night. He had been having loose stools, two to four a day, for three weeks. His appetite was good and he did not feel really ill. On examination he was found to have severe oedema, specially affecting the legs, scrotum, and back. There was some free fluid in the abdomen. The heart was apparently normal except that the pulmonary second sound was a little loud. The pulse-rate was 76 and the blood-pressure 140/90. The tendon reflexes were brisk in the arms and legs. He was given 20 mg aneurin intravenously on the first

difficult, in the majority the clinical manifestations suggested that the condition was distinct from beriberi and it is hoped that this will be demonstrated. The number of men suffering from oedema was far greater than the numbers given in Table III, which is taken from those referred in consultation. It was usually extremely mild, but accompanied by the annoying symptom of nycturia. No special observations have been made on nycturia, but it was common at this time, and later in the camp's history, when oedema was also common, it was almost universal.

In the majority of cases there was no other symptom than a mild oedema of the ankles and feet in the evening. In a few there was puffiness of the face and ascites. In two cases at least a diuresis produced a fall in weight of over a stone which demonstrated the severity of the pre-existing oedema. One patient (Case 3) had headache and did not feel at all well. When first seen he had fairly severe oedema affecting the legs and face and also some ascites. His blood-pressure was 130/90. The knee and ankle reflexes were brisk. He rested in his room, but by the sixth day was feeling worse and his blood-pressure was 150/90. On the eighth day the oedema was increasing and blood-pressure 140/90. He then took 1 mg of aneurin and 50 mg of ascorbic acid daily, but on the tenth day the oedema was worse and he was admitted to hospital and given 30 gr of potassium citrate three times a day. There was an immediate diuresis and by the fourteenth day his weight had fallen by nearly 20 lb and the blood-pressure was 112/78. He received no other treatment, but remained fairly well though the diet did not improve for over two months. It is improbable that the small dosage of aneurin would have produced this result, and taken with the other cases to be mentioned, the patient was not looked upon as a case of beriberi. The patient demonstrates two points noted in this series, namely, the tendency for the blood-pressure to rise with the onset of oedema and the use of potassium salts in treatment. There was a representative group of average internees who were examined at intervals in order to obtain data about weights, blood-pressure, &c. It was noticed by the medical men doing this work that onset of oedema was accompanied by a rise in blood-pressure. To illustrate this point details of Case 1 are given below.

Date	Weight (lb)	Pulse-rate	Blood-pressure	Oedema
March 27	168	—	101/72	Absent
April 6	166½	92	95/75	Absent
" 20	174½	86	114/87	Present
" 27	181	55	140/90	Present

He was then admitted to hospital with fairly severe oedema. The knee and ankle reflexes were present and the urine free from albumin. He had no significant treatment other than complete rest and the oedema rapidly went down, the following readings were taken.

Date	Weight (lb)	Pulse rate	Blood-pressure
May 5	168	—	130/90
" 10	166½	100	118/90

high and the heart-rate about normal. After aneurin treatment left heart failure developed, which was a sequel noted among the more definite cases described earlier, but only one of the three survived. Their comparative comfort and feeling of well-being when first seen seemed more in favour of a diagnosis of oedema from some other cause. Vedder (1940) described the severe oedema that may occur first in the legs and then in the serous cavities. He stated that pericardial effusion, pulmonary oedema, and hydrothorax are more marked than ascites. Cannon (1929) described the wet type of beriberi, but would look with suspicion on the diagnosis if the knee reflexes were present. Yang and Huang (1934) in their series from Nanking described two interesting patients who were being treated with the resources then available for cardiac beriberi when signs of peripheral neuritis developed and only then did the reflexes disappear. In the very acute cardiac beriberi the knee and ankle reflexes may not be lost, as in two of the earlier patients here described, but these last cases were not of such short duration. Possibly their confinement, leading to little use of the legs, delayed the onset of peripheral neuritis and their lack of exercise may also have delayed the onset of acute heart symptoms. Naturally the death of two out of three internees returned to the camp from military custody caused much anxiety and questioning as to the treatment. Doubt was felt about the diagnosis of beriberi. If the condition was not beriberi there was no indication for aneurin, but if it was then perhaps the rapid administration of the vitamin, by increasing the strain on the left heart in the manner I have already discussed, might in a person extremely ill-nourished and weak have precipitated the fatal attacks. It was decided that should further similar cases occur, the vitamin would be given in small doses, while the patient would be nursed with the utmost care and every effort made to improve his nutrition generally. Whether this would be the best treatment or whether much bigger doses of vitamin should be used remains to be studied.

Series 2 About the same time as the cases of beriberi occurred, oedema was common in the camp and, like the beriberi, disappeared when there was an improvement in the diet in July 1942. The incidence of the two groups is shown in Table III. While there were a few cases where diagnosis was

TABLE III
Monthly Incidence

Month	Beriberi	Nutritional oedema
March	0	1
April	0	5
May	3	10
June	7	8
July	6	11
August	0	6
September	0	1

(The times given are when first examined. This is fairly close to the date of onset of definite symptoms and the exact date of onset of oedema was too unreliable to use.)

oedema here described started in some cases much earlier than this and, in these early cases, no evidence of peripheral neuritis or other typical signs of beriberi developed, although no aneurin was given and the diet did not improve until the second half of July. At least one patient developed oedema in spite of adequate prophylactic doses of aneurin. The slight cardiovascular changes noted were not those of beriberi, and improvement occurred without vitamin therapy. The suggestion might be put forward that these were in a very early stage of the type of wet beriberi exemplified by the last three cases of Series 1, but it is difficult to support any diagnosis of beriberi where only one of the three cardinal symptoms of peripheral neuritis, oedema, and heart failure are present. No tests with aneurin were carried out because of the small stocks available. The level of protein in the diet was not so low that it could lead to hypoproteinaemia in a previously well-fed community, and it was concluded that the cause must lie in the change of diet or in some unknown deficiency or imbalance.

Series 3 The remainder of the cases of oedema will be discussed here. After the outbreak described above there was little oedema during the rest of 1942, nor did it occur to any degree in 1943. In May 1944 the camp was moved to a new site and the poor food about this time and the extra energy used in the removal provoked a minor outbreak of oedema. From this time until the camp broke up early in September 1945 oedema was fairly common but rarely severe. The incidence was not estimated, but during the last few months it was in a minor degree almost universal. Usually it was only a little oedema of the feet and shins towards evening, and after the patient had passed urine a number of times during the night had disappeared in the morning. Three or four severe cases were in hospital at the end of internment. One of these whose oedema had increased in spite of taking multiple vitamin tablets had a blood-pressure of 100/70. The tendon reflexes were present. Unfortunately other detailed records of these severe cases are not available. The oedema was worst in the dependent parts, such as the legs and scrotum, and one patient at least had considerable ascites. Treatment was very difficult. One patient had a series of daily injections of aneurin 5 mg without benefit. Two developed diarrhoea which interfered with feeding. Mercurial diuretics produced a temporary increase in the flow of urine, but did not really help. High-protein diet was not given an adequate trial while the patients were under my care. Most of the mild cases seen had oedema as a complication of some other complaint. In some, low blood-pressures were noted, but in at least half they were normal. Potassium salts seemed of some value in treatment, but less than in the previous series. A test was carried out by Dr J P Carlile at this time which is of some interest in relation to this oedema. Four groups of seven men were taken. The first group had apparently no oedema and was given an ounce of salt daily for a week. There was a significant rise in weight and in some cases oedema. A second group of similar patients were used as

Following the experience of Hawes and Vardy (1935) in Malaya in the control of oedema in nephrosis by the administration of potassium salts, this treatment was tried in these cases of nutritional oedema. The dosage given was 30 gr three times a day. Other instructions given to patients were to rest with the feet up as much as possible and avoid excess sodium chloride and fluid. Examples of successful treatment are given in Table IV.

TABLE IV
Nutritional Oedema

Case 2

Day	Weight (lb)	Pulse-rate	Blood pressure	Treatment
1st	163	—	140/80	Ascorbic acid and reduction in salt intake
15th	150½	64	120/70	—
23rd	150½	—	—	Potassium citrate
32nd	150½	76	94/60	—

(He relapsed 6 weeks later just before diet improved)

Case 4

1st	155½	—	140/75	Potassium acetate
8th	146½	—	118/58	—

Case 5

1st	168½	—	155/85	Potassium acetate
6th	163	—	120/65	—

Case 6

1st	110	96	160/85	Potassium acetate
7th	108	76	140/60	—

(This patient had a very forcible action of the heart and tachycardia at first)

Case 7

1st	187½	88	140/90	Potassium chloride
10th	183½	88	120/70	—

Case 8

1st	165	48	125/70	Potassium citrate
5th	158½	—	120/75	—

(This man had taken some anourin earlier in internment, but the quantity is unknown)

Case 9

1st	178	60	135/82	Potassium citrate
5th	164½	60	132/75	—
11th	159½	60	110/68	—

(The history of oedema in this case was only three days. The patient was in the habit of taking a little more sodium chloride than other internees. He had also taken prophylactic anourin and ascorbic acid. In the case of the former this had amounted to about 1 mg daily during internment.)

Since this oedema occurred at the same time as typical beriberi it is necessary to review the points in the differential diagnosis. The first cases of beriberi dated their symptoms from the middle of May, that is, after three months' internment. This is in keeping with the observation of Fraser and Stanton (1909) that beriberi did not occur in any of their patients who had been on white rice for a period less than 87 days. The form of nutritional

MEPACRINE AND FALCIPARUM MALARIA¹

By JAMES REID

Introduction

THE entry of Japan into the World War in 1941 soon created an emergency in malaria control, for our armies had to campaign in highly malarious parts of the world while our main natural resources of quinine were no longer open to us. The emergency was met, firstly, by collecting and conserving all available stocks of quinine, and secondly, by the concentrated effort of our chemists to find and manufacture an efficient synthetic substitute. This latter work went on simultaneously both in Britain and in the United States of America. Before the war, German chemists had produced the synthetic drug atabrin, which was quickly proved to be effective in the treatment of the main types of malaria, and probably even superior to quinine in the prevention of the disease (Bull. Health Organ., League of Nations, 1937). However, reports of serious toxic reactions after its use enjoined some caution (Kingsbury, 1934; Field, Niven, and Hodgkin, 1937), and before the war atabrin had by no means superseded quinine. The pressing need for an anti-malarial drug led to attempts to manufacture a substitute on a large scale, and Imperial Chemical Industries produced mepacrine which was claimed to be the same as German atabrin. The same drug, produced in American laboratories, was first named atabrine and later quinacrine. Mepacrine was available for trial in the British Army early in 1943 when the investigations to be described were also begun. The objects of the experiments were to assess the value of mepacrine as a preventive of falciparum (malignant tertian or subtertian) malaria, to determine its optimum dosage, and to discover the margin between effective therapy and the production of toxic effects.

Older methods of investigating the therapeutic action of a new drug generally took a long time, as they involved giving progressively increasing doses of the drug to a large number of patients suffering from the disease for which a remedy was sought. Moreover, this method always suffered from the drawback of the great variation in individuals both as regards absorption of the drug and the clinical response to treatment. In 1943 speed was everything and only a small number of volunteers was available for therapeutic trials. A different line of approach was clearly essential and a clue had fortunately been given by recent extensive studies of the sulphonamides. It was recognized that to ensure an effective therapeutic response a certain concentration of sulphonamide in the blood and body fluids must be reached and maintained. Estimation of sulphonamide concentration in body fluids

¹ Received November 29, 1946

controls A third group who had oedema in the evenings received aneurin 1 mg by injection daily for one week, and a fourth group similar to the third was used as control There was no significant change in weight in these last three groups Clinical records are inadequate to allow of discussion of this series, but it is probable that the oedema was due to hypoproteinaemia A long-continued diet of poor quantity and quality was having its effect

To complete this survey one must record the results of increased diet at the end of hostilities At first the diet was increased largely by the addition of rice In many men oedema became worse at this time Later, on the voyage to England when multiple vitamin tablets were being taken and the diet was high in protein, a few men not previously much affected by oedema showed considerable swelling of the ankles

I am indebted to the many medical colleagues who worked with me in the Singapore Internment Camp, and particularly to members of the Medical Reference Committee of the camp who supplied particulars of the diet and other information Permission to publish has been kindly granted by Dr W J Vickers, Acting Director of Medical Services, Singapore

Summary

- 1 Three series of cases of oedema in an internment camp are described
- 2 The first series of cases consisted of those diagnosed as beriberi They were much less common than cases of oedema from other nutritional causes Most of the beriberi cases occurred in a period when the supply of vitamin B₁ was low The other patients developed their disease while outside the camp The clinical features are described and the diagnosis discussed
- 3 The second series of cases occurred at the same time as the beriberi, but the clinical appearances were sufficiently different from beriberi to lead to the diagnosis of nutritional oedema from some unknown cause
- 4 The third series occurred towards the end of internment and were probably due to hypoproteinaemia

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All observations were made on healthy volunteers so that unreliable results from marked variation in leucocyte count were not expected, but as an additional check on the blood mepacrine values, urinary mepacrine was also estimated. It was found by experience that the single-extraction method of Brodie and Udenfriend (1943) was reliable for both blood and urinary mepacrine estimations. This method involved extracting the drug from blood into ethylene dichloride, separating the ethylene dichloride and washing with alkali, and then measuring the fluorescent intensity of mepacrine in acidified ethylene dichloride solution. The method had a high degree of specificity associated with excellent extraction recoveries (Brodie and Udenfriend, 1943). Triplicate estimations from the same sample of blood indicated that the constancy of the results was satisfactory (Table I). Later, a Coleman fluorimeter was obtained from America which enabled a direct comparison of blood, plasma, and urinary mepacrine levels to be made on groups of healthy volunteers. When the plasma mepacrine was more than 20 micrograms (μg) per litre, the blood, urine, and plasma mepacrines were directly related to one another (Fig 1), but when the plasma values were less than 20 μg per litre, blood and urinary mepacrine levels continued to be closely related, though plasma values bore no constant relation to either (Fig 2). Since a plasma mepacrine level of 20 μg per litre is about the mean value of a group of healthy individuals taking the usual suppressive doses of 0.1 gm of mepacrine daily, it was concluded that blood mepacrine offered the most reliable index to assess the antimalarial action of the drug in healthy volunteers.

The Chemotherapeutic Action of Mepacrine in Falciparum Malaria²

Fifty-five healthy volunteers taking different doses of mepacrine were inoculated with sporozoites of falciparum malaria to assess the value of the drug as a preventive of malaria, in seven experiments an Italian strain of the parasites was used, in 48 a Roumanian strain. Fifty volunteers were infected by exposure on one to four occasions to the bites of mosquitoes whose salivary glands contained numerous sporozoites. The other five subjects were infected by intravenous injection of a sporozoite-gland-suspension in Locke's solution. An untreated control volunteer who had not previously been exposed to malaria was inoculated along with each group of volunteers taking mepacrine to ensure that the mosquito bites and sporozoite-gland-suspensions were active. Without exception the controls developed a frank attack of malaria with parasitaemia seven to 14 days after sporozoite inoculation, so that absence of malaria in the volunteers taking mepacrine was attributed to the action of the drug.

² This part of the investigation was carried out in collaboration with K. Mellanby, W. D. Nicol, and P. G. Shute. The majority of the volunteers were members of the Friends' Ambulance Unit and Pacifists' Service Unit and were recruited and organized by Dr. Mellanby. Mr. P. G. Shute prepared batches of infected mosquitoes, inoculated the volunteers with malaria, and examined all blood-films for parasites. Dr. W. D. Nicol was responsible for the treatment of the volunteers who developed malaria.

was found to be an effective method of controlling treatment. This technique was now to be applied to mepacrine, and various pointers suggested that it was on the right lines. James (1934) concluded that atabrin must act directly on the malarial parasites because of the rapid changes observed in them soon after administration of the drug to patients with malaria. Shannon, Earle, Brodie, Taggart, and Berliner (1944), working with the new American atabrine, stated that if the drug acted directly on malarial parasites the action was probably related to the concentration of the drug in the plasma. It was thus decided to investigate the relation between the concentration of mepacrine in the blood and its action as a malarial preventive in healthy volunteers who had been inoculated with sporozoites of *falciparum malaria*.

Mepacrine Estimations in Body Fluids

The early work of Shannon, Earle, Brodie, Taggart, and Berliner (1944) demonstrated that the concentration of mepacrine was much greater in cells than plasma. They found that the concentration of mepacrine in leucocytes

TABLE I

Triplicate Estimation of Blood Mepacrine

(Single Extraction Method of Brodie and Udenfriend, 1943)

Sample	Blood mepacrine (μg per litre)			Mean
	1	2	3	
1	71	71	66	69
2	70	65	73	69
3	67	80	67	71
4	75	71	79	75
5	80	80	93	84
6	93	93	80	88
7	87	91	87	88
8	84	100	84	89
9	84	107	84	82
10	131	138	123	130
11	137	133	137	135
12	280	291	286	285

was more than 400 times that in plasma, and even in plasma 80 to 90 per cent of the drug was probably 'bound' to protein. In view of the high concentration of the drug in leucocytes, the American workers advocated plasma mepacrine estimations rather than whole blood estimations, because marked variation in the leucocyte count might give unreliable results when estimations were made with whole blood. The method of estimation introduced by Brodie and Udenfriend (1943) and used by us required a sensitive fluorimeter of the Coleman type. When our work started no suitable fluorimeter was available in Britain capable of determining the minute quantities of mepacrine in plasma that resulted from the small doses of the drug required to prevent malaria. We had therefore to make use of the high concentration of mepacrine in leucocytes, and estimate the level of the drug in whole blood, to enable us to be well within the range of sensitivity of a Hilger fluorimeter.

not requiring bed-treatment to incapacitating reactions that were indistinguishable clinically from an acute attack of malaria. The minor effects were mainly malaise and headache often diagnosed by the men themselves as the 'start of a cold in the head', but a nasal discharge, the usual sign of acute coryza, did not appear. The severe reactions were characterized by sensations

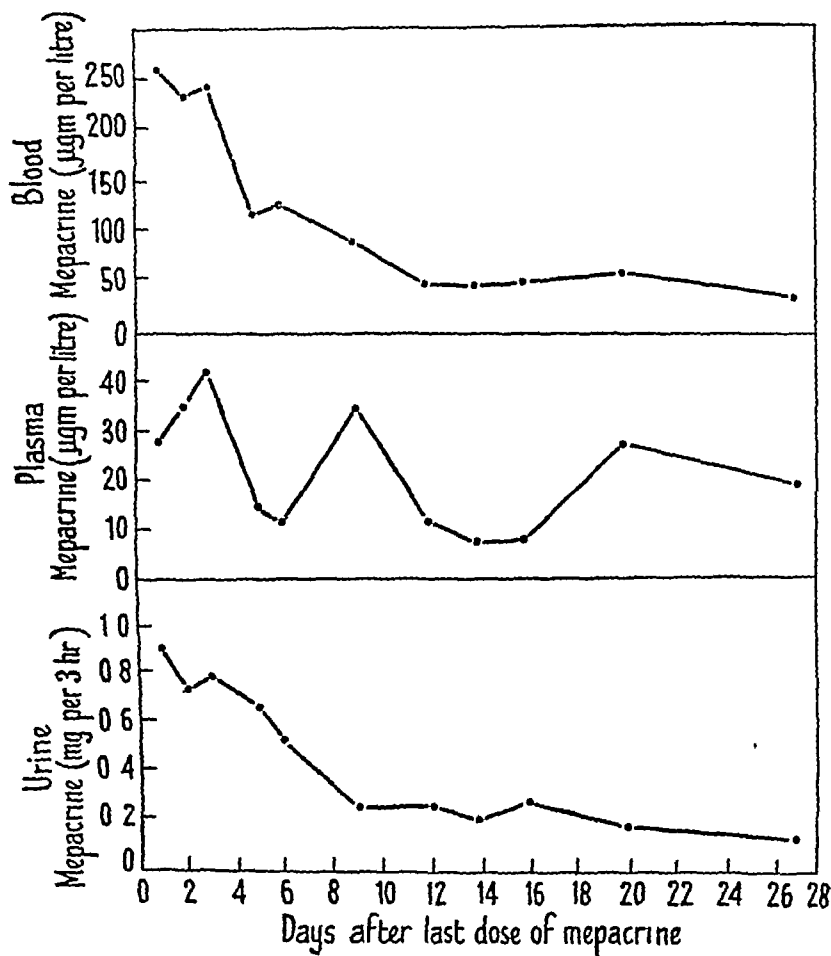


FIG 2 The fall in the mean blood, plasma, and urinary mepacrine of a group of 10 healthy soldiers after they had been given 3.4 gm of mepacrine in seven days

of cold followed by feelings of warmth, accompanied by occipital headache, pain behind the eyes, and pain in the neck, back, and limbs. All grades of severity between minor and severe reactions were encountered. A complete explanation of the transient fever was obviously desirable. Had it anything to do with malaria or was it due to some intercurrent infection? The possibility of an intercurrent infection was first considered, but no common complaint in Britain without localizing signs in the chest or elsewhere fitted into the symptomatology. Moreover, the incidence of the fever was the same

Reactions to sporozoite inoculation of volunteers taking mepacrine. Thirteen of the 55 volunteers developed malaria with parasitaemia nine to 24 days after sporozoite inoculation. Twenty others had a curious transient fever at the same interval after sporozoite inoculation, but parasites were not found after careful search of thick blood-films. The remaining 22 volunteers were

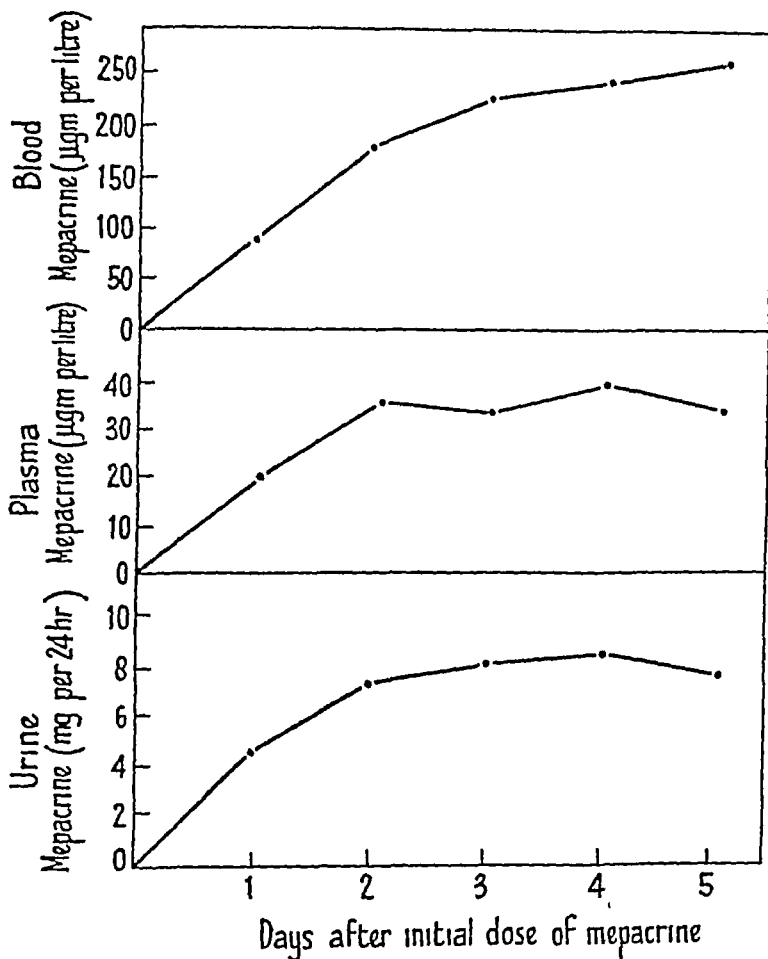


FIG. 1. The mean blood, plasma, and urinary mepacrine of a group of eight healthy soldiers who were given an initial dose of 0.6 gm. of mepacrine followed by daily doses of 0.3 gm. for three days.

symptom-free and had no fever in the three months after sporozoite inoculation. The transient fever, in which the temperature ranged from 100° to 103° F, requires special consideration. In 15 volunteers it was only of one day's duration and was characterized by a rapid rise to a peak and an equally rapid fall. In five other instances the fever was remittent or intermittent and two or three temperature peaks were recorded over two to six days. The symptoms accompanying this fever varied in severity from minor effects

or four weeks afterwards, but at the same time they bring out the difficulties and limitations of assessing the value of the drug on the simple basis of dosage by mouth. It is true that the number of volunteers in each group was too small to allow firm conclusions to be drawn, but even more unsatisfactory is the absence of explanation of why some volunteers remained symptom-free,

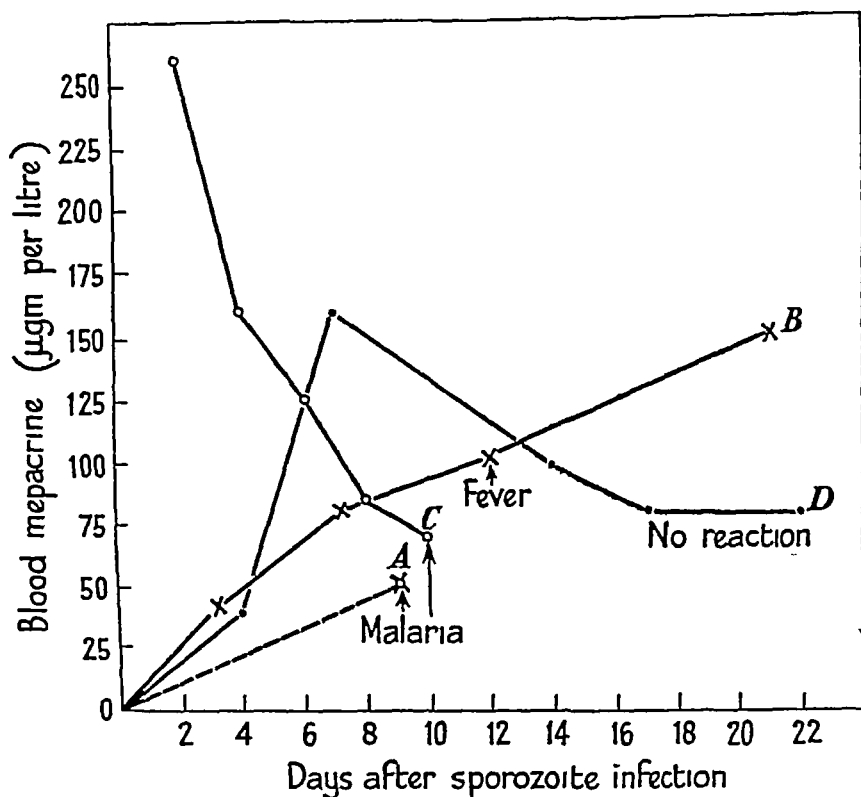


FIG 3 The blood mepacrine levels of four volunteers, A, B, C, and D, at intervals in the incubation period of falciparum malaria are shown. A high blood level of the drug eight to 12 days after sporozoite inoculation was more important in preventing malaria and transient fever than a high level just after inoculation.

some developed malaria, and some transient fever, when all were receiving the same doses of the drug. It was obvious therefore that simple dosage experiments had a limited value, so observations on blood levels of mepacrine were also made.

Blood mepacrine levels in relation to the prevention and occurrence of malaria
Blood mepacrine levels of 27 volunteers taking the drug were estimated at intervals after sporozoite inoculation by the single-extraction method of Brodie and Udenfriend (1943). Samples of blood were always taken 24 hours after the daily dose of mepacrine so that the minimum daily blood-levels might be determined. The volunteers were divided into groups who took the same doses of the drug and were inoculated with sporozoites at the same

in winter and summer, and other volunteers, not yet experimentally inoculated but living under exactly the same conditions, were unaffected. From the fact that the transient fever occurred just at the interval after inoculation when a genuine attack of malaria would be expected, the provisional inference was drawn that the fever was actually malaria suppressed by mepacrine. Experimental proof that this inference was correct was provided by the successful transmission of malaria with obvious parasitaemia to a volunteer by injection of blood taken at the onset of transient fever. The occurrence of transient fever in volunteers inoculated with sporozoites and treated with mepacrine, and the correct interpretation of its significance, is a matter of great practical importance. The experimental facts suggest strongly that many of the short fevers which were so frequent among our troops who were taking mepacrine daily and were campaigning in highly malarial regions were really suppressed attacks of malaria.

Dose of mepacrine in relation to the prevention or occurrence of malaria. Four groups of volunteers taking different doses of mepacrine were inoculated with sporozoites of *falciparum malaria*. Two groups were given 0.1 gm of mepacrine daily for three to four weeks after sporozoite inoculation. Dosage started on the day of sporozoite inoculation in one group, while in the other group dosage had begun one month before inoculation. The other two groups were given a loading dose of 1.0 gm in the three days preceding sporozoite inoculation, followed by 0.1 gm daily for two to five days and for 22 days respectively after inoculation. The loading dose was divided as follows, 0.1 gm on the first day, 0.3 gm on the second, and 0.6 gm on the third. By these experiments it was hoped to decide whether there was any advantage in giving mepacrine before sporozoite inoculation, and whether administration of the drug must be continued after inoculation in order to prevent malaria. The results were as follows:

Group 1. Six volunteers were given 0.1 gm of mepacrine daily for 20 days. The first dose was given on the day of inoculation with sporozoites. Two volunteers developed malaria, two had transient fever, and the other two had no reaction.

Group 2. Twenty-five volunteers were given 0.1 gm of mepacrine daily for about a month before and for one month after sporozoite inoculation. One volunteer had malaria, 11 had transient fever, and 13 remained symptom-free.

Group 3. Five volunteers were given a loading dose of 1.0 gm of mepacrine in the three days preceding sporozoite inoculation and 0.1 gm daily for the next two to four days. All five developed malaria.

Group 4. Seven volunteers were given a loading dose of 1.0 gm of mepacrine in the three days preceding sporozoite inoculation and 0.1 gm daily for the next 22 days. Two had transient fever and five had no reaction. Malaria did not occur.

These experiments suggest that the best way to prevent malaria is to start mepacrine dosage before experimental inoculation and continue it for three

or four weeks afterwards, but at the same time they bring out the difficulties and limitations of assessing the value of the drug on the simple basis of dosage by mouth. It is true that the number of volunteers in each group was too small to allow firm conclusions to be drawn, but even more unsatisfactory is the absence of explanation of why some volunteers remained symptom-free,

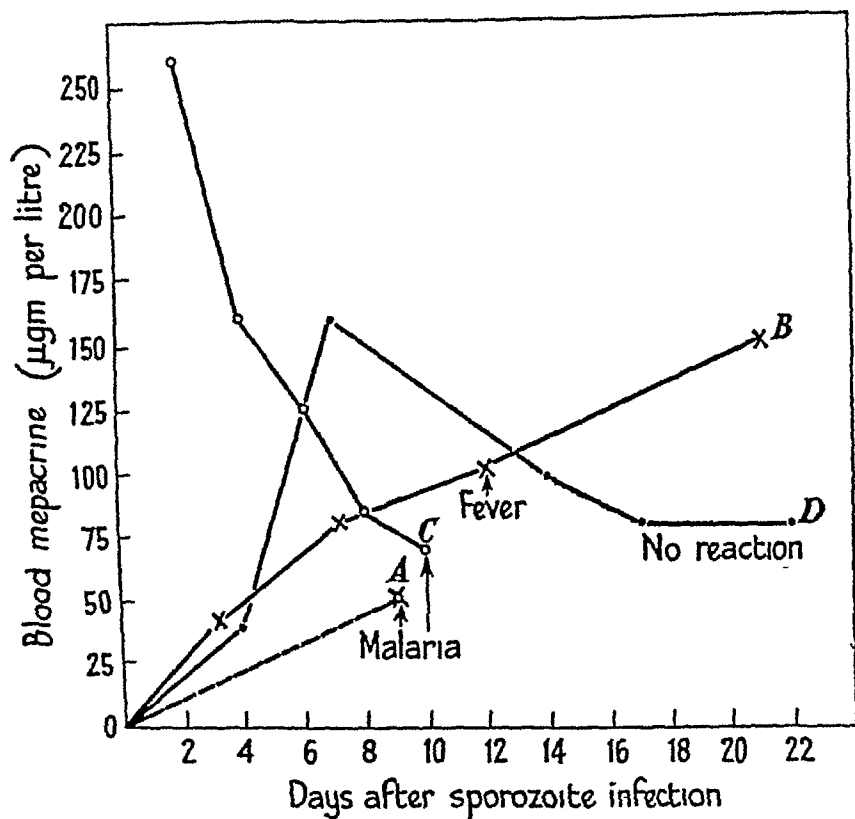


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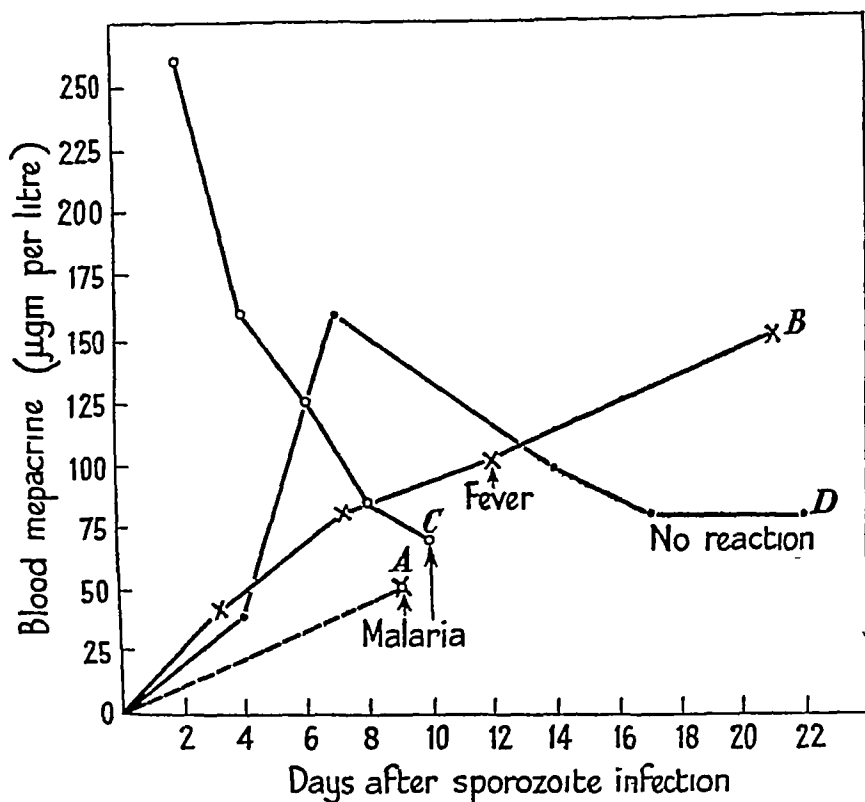


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time The relation between blood mepacrine and the prevention or occurrence of malaria was investigated by comparing the levels of mepacrine in the blood of volunteers who developed malaria with those of volunteers who escaped the disease In a preliminary experiment it was found that the blood mepacrine level at the time of sporozoite inoculation had no significant

TABLE II
Blood Mepacrine and Malaria

Group	Total number of volunteers	Malaria cases		Others	
		Number	Blood mepacrine (μg per litre)	Number	Blood mepacrine (μg per litre)
A	6	1	77	5	150, 230, 254, 225, 337
B	3	2	53 60	1	113
C	8	6	10 20 20 40 40 64	2	100, 120
D	3	1	20	2	220, 260
E	2	2	26 70	0	—
F*	5	0	—	5	220, 360, 300, 316, 286 (7 days) — 480, 448, 240, 520 (14 days) 248, 680, — 420, 408 (20 days)

* Group F had no malarias, but the blood levels at seven days, 14 days, and 20 days after infection are shown for comparison with the others It will be noted that the levels at these times were always more than 100 μg per litre

influence on the course of events, but the levels towards the end of the expected incubation period decided whether or not malaria supervened (Fig 3) The blood mepacrine levels of the malarias in each group of volunteers, just before the onset of fever, were invariably much lower than the levels in the volunteers who escaped the disease (Table II) The levels in the 12 malarias ranged from 10 to 77 μg per litre, the levels in the other volunteers ranged from 100 to 337 μg per litre It thus seemed clear that malaria prevention depended on the level of mepacrine in the blood just before the onset of the disease, and that a level of at least 100 μg per litre must be maintained for effective suppression of the disease

With regard to transient fever, some interesting facts emerged in relation to the blood mepacrine levels When these febrile attacks were first noticed in our volunteers their significance was not appreciated, and only a few blood mepacrine estimations were made because previous work had suggested that variation in leucocyte count during fever might invalidate the results However, when the blood mepacrine levels were compared in the same volunteer before and after transient fever it was found that the nearer to the

actual onset of fever that estimations were made the lower were the blood mepacrine levels and, conversely, the nearer to the day of subsidence of fever that observations were made the higher were the blood mepacrine (Table III) The rise in blood mepacrine induced by fever suggested at once the following explanation for the self-limiting character of transient fever In both frank

TABLE III
Blood Mepacrine and Fever

Volunteer	Before fever Number of day(s)	Blood mepacrine (μ g per litre)	After fever Number of day(s)	Blood mepacrine (μ g per litre)
1	1	15	5	100
2	1	52	2	228
3	2	52	2	100
4	3	150	1	288
5	5	224	2	760

malaria and transient fever the blood mepacrine is sufficiently low before the onset of fever to allow parasites to develop In malaria the blood-level continues to remain low and parasitaemia becomes obvious In transient fever the blood mepacrine rises to a level that is lethal to parasites and so fever quickly subsides and parasites are not found in blood-films

The cause of the rise in blood mepacrine during fever also required explanation and several possibilities were considered, (1) increased absorption of the drug during fever, (2) leucocytosis during fever, and (3) alteration in the partition of the drug between the blood and tissues Increased absorption was ruled out because the rise in blood mepacrine occurred in some volunteers several days after the last dose of the drug had been given A febrile leucocytosis was also eliminated as a major cause because similar changes in both urinary and plasma mepacrine were found to accompany fever in two other volunteers The rise in blood mepacrine during fever was therefore thought to be due to an alteration of the partition of the drug between the blood and tissues In other words, the blood mepacrine increased at the expense of the tissue stores of the drug as a result of the fever

The efficacy of routine Army dosage for malaria prevention The experiments already reported have shown that for the prevention of malaria in our volunteers a minimum blood mepacrine level of 100 μ g per litre, just before the onset of malaria, was required When the actual onset of malaria cannot be predicted, as with natural infections in the field, a minimal daily blood-level of 100 μ g per litre must be maintained for the effective control of the disease The routine dose of mepacrine employed by the Army for this purpose was 0.1 gm daily An estimate of the efficacy of this régime was made by giving this daily dose to 11 volunteers and estimating the resulting blood and urinary mepacrine levels for a prolonged period Observations were made continuously on 11 men for two months, but then the total number available diminished until after five and a half months only four of the original 11 volunteers remained Samples of blood for mepacrine estimations

were taken immediately before the daily dose of drug, and urinary mepacrine were determined in the urine excreted in the three hours immediately preceding the daily dose. The individual results are shown in Figs 4 and 5. There was considerable variation in the blood and urinary mepacrine levels of different individuals, but those with high blood mepacrine levels tended to

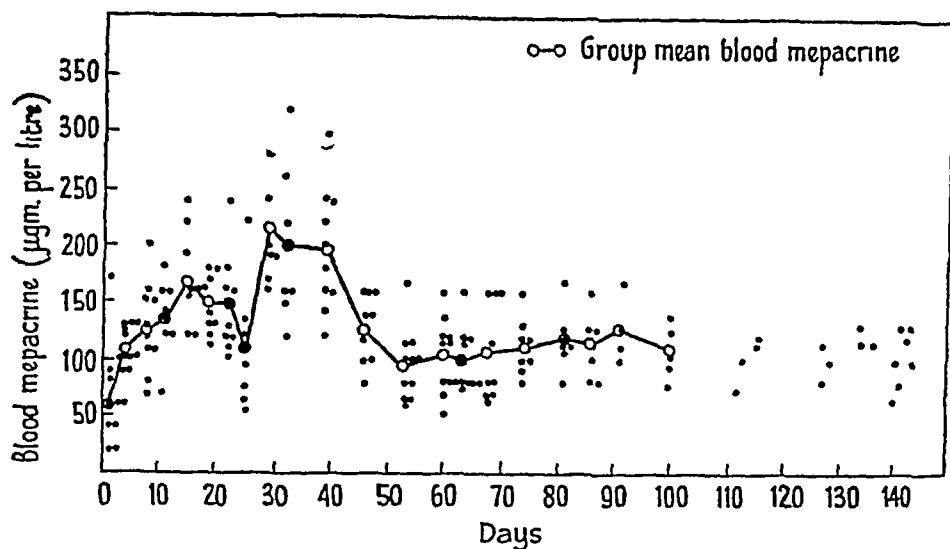


FIG 4 The individual blood mepacrine levels and the mean level of a group of volunteers who were given 0.1 gm. of mepacrine daily

have high urinary levels, and those with low blood-levels tended to have low urinary levels, so that the mean values of the group reflected the changes in each individual fairly accurately. The mean blood mepacrine level increased each day until a peak level of 167 μg per litre was reached on the 15th day of dosage. The level then fell to 109 μg per litre on the 22nd day and increased to reach a second peak of 215 μg per litre on the 29th day. Thereafter, in spite of the continuous mepacrine administration it fell to 93 μg per litre on the 53rd day. From then onwards a fairly stable level was maintained ranging from 100 to about 130 μg per litre. Similar changes were observed in the mean urinary mepacrine of the group, except that the first peak level was higher than the second. This was largely due to an abnormally high urinary mepacrine value in one subject at the time of the first peak. Over the period of investigation about one-third of the blood mepacrine values were less than 100 μg per litre, so that in the light of the previous conclusion that a minimal daily blood mepacrine level of 100 μg per litre is necessary to prevent malaria, a high incidence of transient fever (specially after the first seven weeks of dosage) would be expected in men continuously exposed to infection. This view agrees with our actual findings in 25 volunteers who took 0.1 gm. of mepacrine daily for about a month before and after experimental inoculation with sporozoites. One volunteer

developed malaria, 11 had transient fever, and 13 remained symptom-free. The experiments therefore suggest that the routine daily dose of 0.1 gm. of mepacrine, while it confers a considerable degree of protection from malaria, is not ideal. A larger daily dose of mepacrine, if well tolerated, would raise the blood mepacrine level and would be expected to eliminate transient fever.

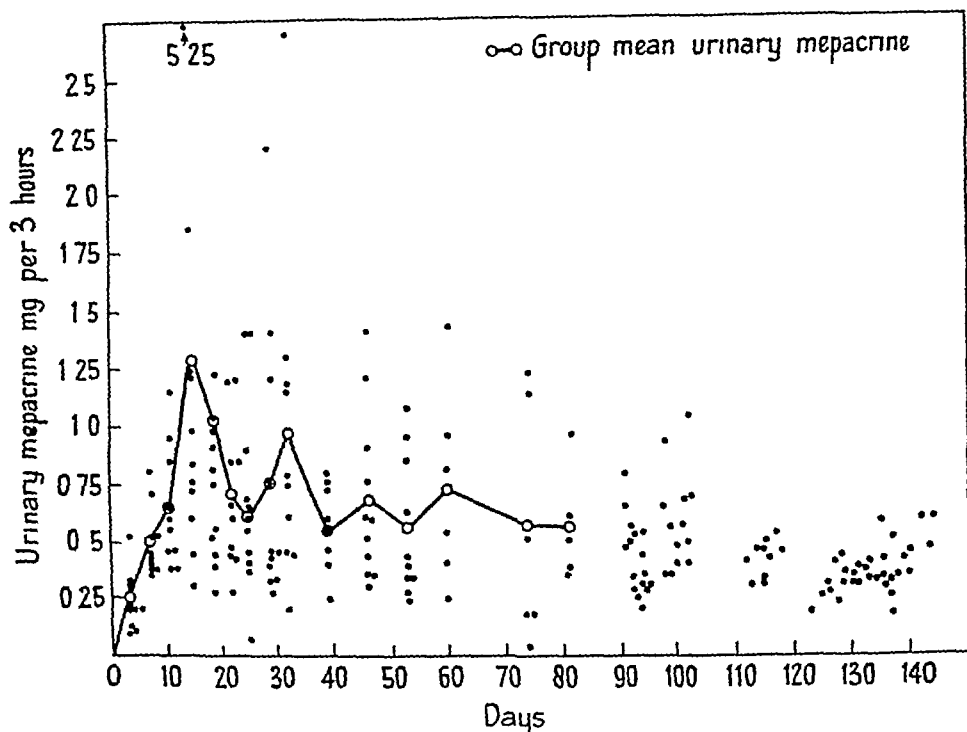


FIG. 5. The individual urinary mepacrine levels and the mean level of a group of volunteers who were given 0.1 gm. of mepacrine daily.

or at least reduce its incidence to insignificant proportions. Unfortunately, no real estimate of the incidence of transient fever in soldiers taking the routine dose of mepacrine for malaria prevention in the recent war is possible. Notification of all pyrexias in the field were made from hospitals, and as difficulties of communication were a major problem in the Far East, the majority of transient fevers probably cured themselves on the way to hospital and so were not notified. Moreover, patients were detained in hospital for 48 hours before notifications were made so that they had an additional two days in which to get well. A pointer to the seriousness of the problem may be gleaned from the need to create Malaria Forward Treatment Centres for the treatment and disposal of 'pyrexias of unknown origin'.

The most important observation in this part of the investigation was the fall in blood and urinary mepacrine levels in spite of continuous administration of the drug. This observation implied that after a time the drug was no longer being satisfactorily absorbed from the intestine or that the process

of degradation of the drug in the body was accelerated. These implications were of obvious practical importance and led to investigations of the fate of the drug in the body.

The fate of mepacrine in the body The amounts of mepacrine absorbed from the intestine during the first six days of dosage, and after the drug had

TABLE IV

Blood, Urine, and Faecal Mepacrine after Prolonged Administration of 0.1 gm. of the Drug Daily

Volunteer	Blood, urine, and faecal mepacrine	Day of dosage					
		63	64	65	66	67	68
1	Blood μ g per litre	160	160	132	160	168	160
	Urine mg per litre	3.9	3.9	2.2	1.2	2.6	2.1
	Urine mg per 24 hrs	5.7	10.1	3.2	4.2	5.1	3.8
	Faeces mg per 24 hrs	18.5	51.5	42.6	—	23.0	35.6
2	Blood μ g per litre	80	100	120	132	100	64
	Urine mg per litre	2.0	4.7	1.4	0.9	2.2	1.5
	Urine mg per 24 hrs	5.8	6.0	2.7	1.9	2.9	3.6
	Faeces mg per 24 hrs	10.7	34.3	40.0	18.7	—	33.3
3	Blood μ g per litre	80	—	132	116	80	116
	Urine mg per litre	3.5	4.7	1.9	—	—	—
	Urine mg per 24 hrs	11.0	7.6	3.5	—	—	—
	Faeces mg per 24 hrs	17.3	52.6	38.3	33.3	22.2	14.3
4	Blood μ g per litre	80	64	100	80	100	72
	Urine mg per litre	1.7	2.2	1.1	1.3	1.2	1.3
	Urine mg per 24 hrs	2.2	2.1	3.9	1.5	3.7	2.1
	Faeces mg per 24 hrs	—	30.1	30.0	20.0	21.0	15.3
5	Blood μ g per litre	116	80	160	116	116	80
	Urine mg per litre	2.4	5.5	1.4	1.1	2.0	1.3
	Urine mg per 24 hrs	4.4	4.6	2.9	3.3	4.7	3.0
	Faeces mg per 24 hrs	2.7	35.6	15.1	34.4	20.0	38.5
6	Blood μ g per litre	80	80	120	80	—	72
	Urine mg per litre	—	—	1.1	1.2	1.8	1.1
	Urine mg per 24 hrs	—	—	2.9	2.9	4.9	4.3
	Faeces mg per 24 hrs	10.5	—	51.6	16.4	18.4	17.7
7	Blood μ g per litre	100	72	120	—	—	80
	Urine mg per litre	2.6	3.9	1.9	1.0	2.9	2.4
	Urine mg per 24 hrs	4.5	11.0	2.7	1.6	5.0	3.5
	Faeces mg per 24 hrs	9.3	19.0	—	54.5	22.0	29.0

been taken for about two months, were compared by estimating the mepacrine in the faeces of two groups of volunteers who took 0.1 gm. of the drug daily during the test. One group of four men was taking the drug for the first time and the total amounts of mepacrine in the faeces in six days were 8.5, 11.8, 20.0, and 41.1 mg. respectively. The other group of men had taken 0.1 gm. of mepacrine daily for 62 days preceding the test and the blood mepacrine of all had fallen to relatively stable levels in spite of continuous administration of the drug. The faecal mepacrine were 114.6, 119.4, 131.8, 146.3, 167.0, 167.0, and 172.2 mg. respectively. More mepacrine was therefore present in the faeces after the drug had been taken for about two months than during the first six days. This suggested that less mepacrine was absorbed after prolonged administration of the drug than during the early days of dosage. The next step was an attempt to obtain information on the

importance and extent of degradation of mepacrine in the body. Daily blood mepacrine levels and the total amount of the drug excreted in the urine each day were estimated along with the faecal mepacrine levels of the seven men who had taken the drug for the previous two months. It was hoped that by a process of exclusion 'mepacrine balances' might indicate the importance of drug degradation. The results are shown in Table IV. The blood mepacrine level in each individual showed only minor daily fluctuations during the test period. For practical purposes it may be considered to be constant. The daily dose of mepacrine was therefore required to maintain this stable level. The average amount of mepacrine excreted in the urine in six days was about 25 mg and the average faecal mepacrine in the same period was about 145 mg. The total mepacrine loss in urine and faeces was therefore about 170 mg in six days, on the other hand, the total dose given in this period was 600 mg so that about 430 mg must have been required to maintain the blood mepacrine at a fairly constant level. The only way in which this large amount may be completely accounted for is by some process of degradation of the drug in the body. Drug degradation must therefore be considered when assessing the amount required to maintain an adequate level of mepacrine in the blood. In this connexion it is necessary to distinguish clearly between degradation of mepacrine in the bowel and degradation in tissues after absorption, because mepacrine degraded in the bowel before absorption could have no therapeutic action, whereas mepacrine degraded in tissues has had an opportunity to act on malarial parasites.

Exploratory investigations on the degradation of mepacrine were carried out by *in vitro* tests. The effect of adding mepacrine to the faeces of subjects who had never taken the drug was examined by estimating faecal mepacrine at intervals after the addition of the drug to the faeces. Duplicate or triplicate estimations were always made and the results showed close agreement. The recoveries of mepacrine expressed as a percentage of the amount of drug added were 71, 48, 18, and 14 at three, 24, 48, and 72 hours respectively after the addition of the drug to the faeces. This observation shows that degradation of mepacrine in the intestine is important and that only a part of the dose administered is actually absorbed.

The rate of degradation of mepacrine in the blood was also investigated. A large sample of blood, taken from a volunteer who was receiving mepacrine, was placed in an incubator at 37°C and daily mepacrine estimations were made for the next eight days. The level of mepacrine fell progressively each day from an initial level of 410 µg per litre to 130 µg per litre on the eighth day. The most striking point in this investigation was not the fall, but the fact that the rate of fall in the incubated blood was so similar to that already noted in the blood of volunteers who had ceased to take the drug. Further experiments were undertaken to compare the *in vitro* and *in vivo* rates of fall in blood mepacrine in a group of five volunteers after mepacrine dosage had been stopped. The men were given different doses of mepacrine so that they would have a wide range of blood mepacrine levels when blood was first

of degradation of the drug in the body was accelerated. These implications were of obvious practical importance and led to investigations of the fate of the drug in the body.

The fate of mepacrine in the body The amounts of mepacrine absorbed from the intestine during the first six days of dosage, and after the drug had

TABLE IV
Blood, Urine, and Faecal Mepacrine after Prolonged Administration of 0.1 gm of the Drug Daily

Volunteer	Blood, urine, and faecal mepacrine	Day of dosage					
		03	04	05	06	07	08
1	Blood μ g per litre	160	100	132	160	168	160
	Urine mg per litre	3.0	3.9	2.2	1.2	2.6	2.1
	Urine mg per 24 hrs	5.7	10.1	3.2	4.2	5.1	3.8
	Faeces mg per 24 hrs	18.5	51.5	42.6	—	23.0	35.6
2	Blood μ g per litre	80	100	120	132	100	64
	Urine mg per litre	2.0	4.7	1.4	0.9	2.2	1.5
	Urine mg per 24 hrs	5.8	6.0	2.7	1.9	2.9	3.6
	Faeces mg per 24 hrs	10.7	34.3	40.0	18.7	—	33.3
3	Blood μ g per litre	80	—	132	116	80	116
	Urine mg per litre	3.5	4.7	1.9	—	—	—
	Urine mg per 24 hrs	11.0	7.6	3.5	—	—	—
	Faeces mg per 24 hrs	17.3	52.0	38.3	33.3	22.2	14.3
4	Blood μ g per litre	80	64	100	80	100	72
	Urine mg per litre	1.7	2.2	1.1	1.3	1.2	1.3
	Urine mg per 24 hrs	2.2	2.1	3.0	1.5	3.7	2.1
	Faeces mg per 24 hrs	—	30.1	30.0	20.0	21.0	15.3
5	Blood μ g per litre	116	80	160	116	116	80
	Urine mg per litre	2.4	5.5	1.4	1.1	2.0	1.3
	Urine mg per 24 hrs	4.4	4.0	2.9	3.3	4.7	3.0
	Faeces mg per 24 hrs	2.7	35.6	15.1	34.4	20.0	38.5
6	Blood μ g per litre	80	80	120	80	—	72
	Urine mg per litre	—	—	1.1	1.2	1.8	1.1
	Urine mg per 24 hrs	—	—	2.9	2.9	4.9	4.3
	Faeces mg per 24 hrs	10.5	—	51.6	16.4	18.4	17.7
7	Blood μ g per litre	100	72	120	—	—	80
	Urine mg per litre	2.6	3.0	1.9	1.0	2.9	2.4
	Urine mg per 24 hrs	4.5	11.0	2.7	1.6	5.0	3.5
	Faeces mg per 24 hrs	9.3	19.0	—	54.5	22.0	29.0

been taken for about two months, were compared by estimating the mepacrine in the faeces of two groups of volunteers who took 0.1 gm of the drug daily during the test. One group of four men was taking the drug for the first time and the total amounts of mepacrine in the faeces in six days were 8.5, 11.8, 20.0, and 41.1 mg respectively. The other group of men had taken 0.1 gm of mepacrine daily for 62 days preceding the test and the blood mepacrine of all had fallen to relatively stable levels in spite of continuous administration of the drug. The faecal mepacrine were 114.6, 119.4, 131.8, 146.3, 167.0, 167.0, and 172.2 mg respectively. More mepacrine was therefore present in the faeces after the drug had been taken for about two months than during the first six days. This suggested that less mepacrine was absorbed after prolonged administration of the drug than during the early days of dosage. The next step was an attempt to obtain information on the

hydrogen-ion concentration diminished the amount of mepacrine 'bound' to protein, while a decrease augmented it. The change in partition was critical about pH7 which suggests that pH may be important in altering the partition of the drug within the body between tissues and the blood. The increase of acid metabolites which is known to occur in tissues during febrile diseases

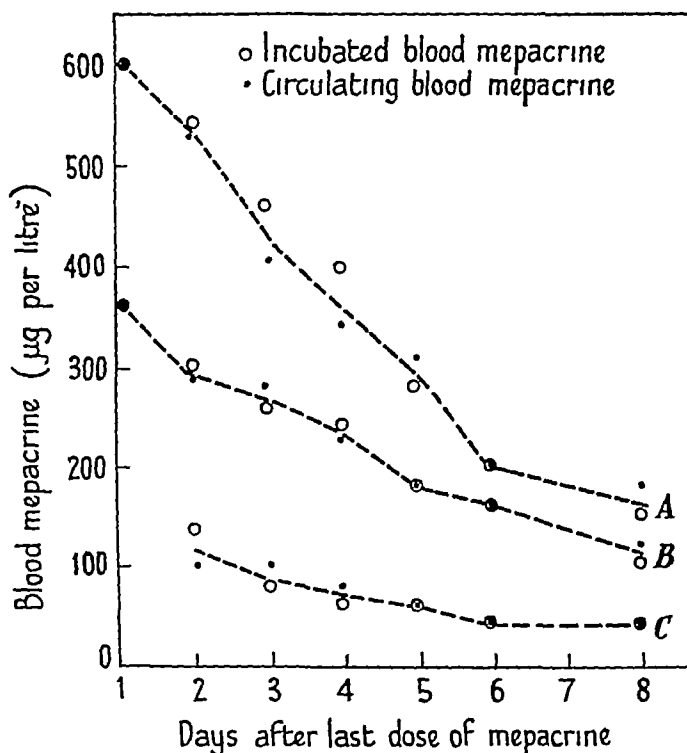


FIG 6 The rate of fall in the mepacrine level in circulating blood after dosage was stopped was the same as the rate of degradation in incubated blood, and both rates were directly related to the initial concentration of the drug in the blood

may therefore be partly responsible for the rise in blood mepacrine that was found in the transient fevers

Mepacrine Toxicity

Abdominal colic, vomiting, diarrhoea, muscle cramps, epilepsy, and psychosis have all been attributed to the administration of mepacrine to patients with malaria, but, as many of these alleged toxic effects are encountered in malaria itself, it is not possible to decide to what extent the disease and to what extent the drug is responsible. Toxic reactions developed in some of the healthy volunteers who were taking mepacrine but were not inoculated with malaria. These reactions were almost certainly due to mepacrine and their relation to the concentration of the drug in the blood and urine has

withdrawn Large samples of blood were taken 24 hours after the last dose of mepacrine, they were divided into 5 c.c. specimens and placed in sterile extraction bottles in an incubator at 37°C The mepacrine content of the incubated blood was estimated each day for one week except on the sixth day The blood mepacrine of the volunteers were estimated at corresponding

TABLE V
Degradation of Mepacrine in Incubated and Circulating Blood

Day	Blood mepacrine (μ g per litre)									
	Volunteer 1		Volunteer 2		Volunteer 3		Volunteer 4		Volunteer 5	
	C B	I B	C B	I B	C B	I B	C B.	I B	C B	I B
1	630	600	530	540	380	410	290	300	100	140
2	420	400	410	460	320	320	280	260	100	80
3	350	360	340	400	240	250	230	240	80	60
4	290	320	310	280	220	200	180	180	60	60
5	160	140	200	200	200	200	160	160	40	40
7	120	120	180	150	160	160	120	100	40	40

C B - Circulating blood

I.B - Incubated blood

times The similarity in the rate of fall in incubated blood and in circulating blood was striking (Table V), and for practical purposes may be considered to be the same Moreover, it was found that the rate of fall of mepacrine in both circulating and incubated blood depended on the initial level of the drug in the blood The higher the initial level the more rapid was the rate of fall (Fig 6) Thus it is suggested that the fall in circulating blood mepacrine is almost wholly due to degradation of the drug, since the loss of drug through the main channel of excretion, the urine, is insignificantly small in comparison with the total amount of drug which has disappeared This suggestion, if correct, implies that the rate of degradation in the tissues is also proportional to the concentration of the drug in the tissues, since the blood level of the drug is wholly dependent on replenishment from the tissue stores after dosage has stopped

These experiments emphasize the importance of the breakdown of mepacrine, both in the alimentary tract and within the body, in determining the level of the drug in the blood The only other problem that required consideration was the partition of the drug between the blood and tissues The rapid rise in blood, plasma, and urinary mepacrine which accompanied transient fever in the volunteers inoculated with sporozoites suggested that the short fever by itself altered the partition Direct investigation of this problem was not practicable because it would have involved repeated biopsies, but experiments to investigate possible factors that might influence the partition of mepacrine were carried out *in vitro* in a simple denatured eggwhite-water preparation The effect of temperature, pH, and electrolyte concentration on the amount of mepacrine 'bound' to the denatured protein was examined Temperature and electrolyte concentration had no significant influence on the partition, but pH had a pronounced effect An increase in

hydrogen-ion concentration diminished the amount of mepacrine 'bound' to protein, while a decrease augmented it. The change in partition was critical about pH7 which suggests that pH may be important in altering the partition of the drug within the body between tissues and the blood. The increase of acid metabolites which is known to occur in tissues during febrile diseases

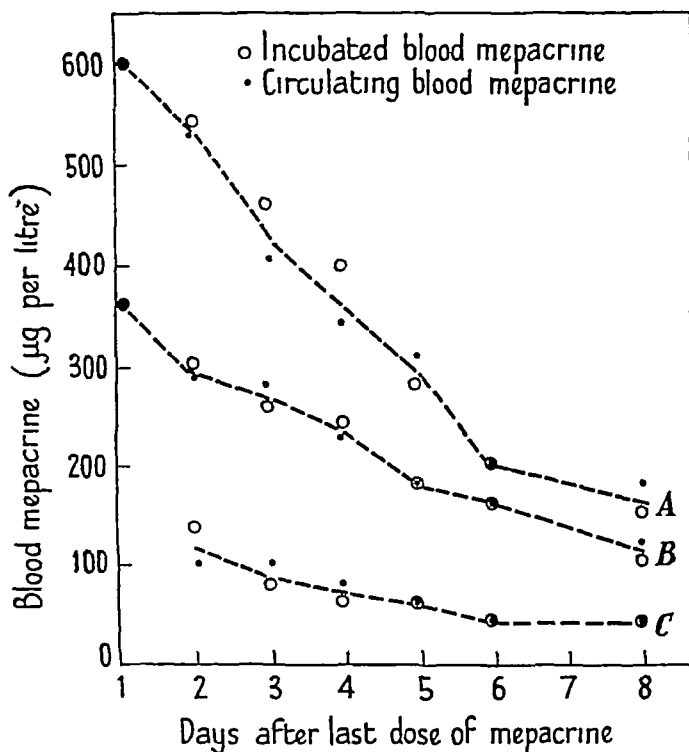


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been examined. The acute toxic symptoms that were encountered were of three types.

1 Mild symptoms such as headache, nausea, epigastric discomfort, and minor visual disturbances. They were frequent, but never sufficiently severe to interfere with ordinary duties. They occurred both after large doses of mepacrine (0.5 gm) and after the usual routine doses (0.1 gm). It was found

TABLE VI
Blood Mepacrine and Fluid Intake

	Blood mepacrine (μ g per litre)						
Volunteer	$\frac{1}{2}$ hr	$\frac{3}{4}$ hr	2 $\frac{1}{2}$ hrs	5 hrs	10 hrs	14 $\frac{1}{2}$ hrs	23 hrs
Restricted fluid intake group							
109	133	217	167	433	233	333	250
110	150	217	133	187	150	283	317
111	133	192	180	233	258	517	767
112	141	192	260	173	125	300	433
113	133	242	120	193	233	583	633
114	150	208	127	103	167	333	383
Group mean	140	211	164	235	194	392	463
Liberal fluid intake group							
115	150	208	193	140	167	450	633
116	150	350	153	187	167	333	433
117	183	217	153	233	158	267	467
118	175	183	127	147	158	267	467
119	167	183	253	173	83	200	317
120	175	217	133	187	158	367	600
Group mean	166	226	169	178	148	314	486

that when small doses were continued symptoms soon disappeared and did not recur.

2 Alimentary symptoms such as vomiting, colic, and diarrhoea. These were often severe and incapacitating and, on one occasion, gave rise to considerable anxiety when they assumed almost epidemic proportions in troops on active service. Investigation of their cause was therefore carried out to see if they could be explained and avoided, and a clue came from direct observation in the field that they did not occur when sufficient water was taken with each dose of mepacrine. Two groups of six volunteers were given the same doses of mepacrine at the same times, but in one group the fluid intake was restricted for three days previously, whereas in the other group liberal quantities of fluid were given. In the first group the urinary output on the day of the test ranged from 240 to 900 c.c. A large dose of mepacrine, 1.4 gm in 15 hours, was given to all, divided as follows, initial dose 0.2 gm, after five hours 0.3 gm, after 10 hours 0.4 gm, and after 15 hours 0.5 gm. In five out of six volunteers whose fluid intake was restricted diarrhoea with loose watery stools and colic ensued, in the other group these symptoms were completely absent. Frequent estimations of the blood mepacrine level were carried out during the day of test, and the urinary output in the 24 hours after the initial dose was also determined. The results are shown in Tables

VI and VII The mean blood mepacrine levels did not vary much in the two groups, but much less mepacrine was excreted in the urine of the group whose fluid intake was restricted. The difference was quite clearly associated with the diminished output of urine. From this experiment the inference was drawn that the observation in the field was correct, and that the free use of water is important in preventing alimentary symptoms from mepacrine.

TABLE VII
Urinary Mepacrine and Fluid Intake

Volunteer	Urine		
	Volume in c c per 24 hrs	Mepacrine (mg per litre)	Mepacrine (mg per 24 hrs)
Restricted fluid intake group			
109	240	3.6	0.9
110	440	5.3	2.3
111	720	6.6	4.7
112	900	10.3	9.3
113	780	2.6	1.9
114	900	11.0	9.9
Group mean	660	6.6	4.8
Liberal fluid intake group			
115	2,100	8.6	18.1
116	2,360	9.6	22.6
117	1,800	8.6	15.5
118	1,700	6.6	11.2
119	2,080	6.0	12.5
120	2,400	7.1	17.1
Group mean	2,073	7.7	16.1

3 Severe toxic symptoms that were completely incapacitating. Six medical officers took a single daily dose of 0.5 gm (that is, five times the usual routine dose) of mepacrine for five days while carrying out sedentary duties. Two developed severe toxic symptoms, but the other four were unaffected. Details of the toxic effects were as follows:

Lieutenant I had severe headache a few hours after the first two doses of mepacrine. The headache lasted 11 hours on the first day and three hours on the second day. Immediately after the third, fourth, and fifth doses he was perfectly well and had no complaint, but 18 hours after the fifth dose, at 3 a.m. on the sixth day, he was awakened by pain in both loins. He was thirsty, had pain in his tongue, his mouth was dry, and he was sweating profusely. He quenched his thirst, but could not sleep as he felt very excited. At 9 a.m. on the same day he was much improved and reported for examination when he complained of excessive salivation, a bitter taste in his mouth, and thirst. His urine was albumen-free and contained no macroscopic blood. He looked tired and felt out of sorts, but carried out his duties until the afternoon of the seventh day when he had to retire to bed. He was fairly comfortable until evening when pain behind the eyes, pain in the maxilla, and pain in the lumbosacral region radiating down the left leg developed. His pulse rate was 120 and temperature was 101° F. The muscles of both thighs felt tight, and twitchings of bundles of muscle fibres were observed.

been examined. The acute toxic symptoms that were encountered were of three types

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110	150	217	133	187	150	283	317
111	133	192	180	233	258	517	767
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Group mean	140	211	164	235	194	392	463
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118	175	183	127	147	158	267	467
119	167	183	253	173	83	200	317
120	175	217	133	187	158	367	600
Group mean	166	226	169	178	148	314	486

that when small doses were continued symptoms soon disappeared and did not recur

2 Alimentary symptoms such as vomiting, colic, and diarrhoea. These were often severe and incapacitating and, on one occasion, gave rise to considerable anxiety when they assumed almost epidemic proportions in troops on active service. Investigation of their cause was therefore carried out to see if they could be explained and avoided, and a clue came from direct observation in the field that they did not occur when sufficient water was taken with each dose of mepacrine. Two groups of six volunteers were given the same doses of mepacrine at the same times, but in one group the fluid intake was restricted for three days previously, whereas in the other group liberal quantities of fluid were given. In the first group the urinary output on the day of the test ranged from 240 to 900 c.c. A large dose of mepacrine, 1.4 gm in 15 hours, was given to all, divided as follows, initial dose 0.2 gm, after five hours 0.3 gm, after 10 hours 0.4 gm, and after 15 hours 0.5 gm. In five out of six volunteers whose fluid intake was restricted diarrhoea with loose watery stools and colic ensued, in the other group these symptoms were completely absent. Frequent estimations of the blood mepacrine level were carried out during the day of test, and the urinary output in the 24 hours after the initial dose was also determined. The results are shown in Tables

The possibility of chronic toxic effects arising after the drug had been taken for prolonged periods was also of practical importance. Information on this point was obtained by examining repatriated British troops who had taken mepacrine as a malarial preventive for periods of four to 18 months. Disability in these men would not necessarily implicate mepacrine, but

TABLE IX
*Urinary Mepacrine and Severe Toxic Effects after 0.5 gm
Daily for Five Days*

Day	Urinary mepacrine (mg per 24 hrs)					
	Severe toxic effects		No symptoms			
	Case I	Case G	Case C	Case K	Case Cn	Case F
1	4.3	2.1	3.1	3.3	4.9	—
2	3.7	4.2	2.1	3.8	4.5	10.3
3	8.7	5.0	9.5	12.2	4.0	9.3
4	16.2	12.5	18.3	14.1	17.1	16.6
5	20.9	21.5	29.0	20.1	17.8	21.3
6	16.9	14.6	22.7	25.2	4.3	—
7	16.3	12.3	20.6	8.3	13.0	—
8	15.2	2.7	14.8	5.7	5.3	9.8
9	9.2	5.3	14.0	12.9	6.8	3.8
10	10.7	6.0	10.9	7.7	2.5	7.3
11	7.5	3.9	7.0	10.5	4.3	5.7
12	5.2	4.7	5.8	5.6	6.0	6.9

absence of ill effects would provide good evidence that mepacrine taken in suppressive doses for prolonged periods did not create a problem. The results have already been published (Drew and Reid, 1945), and no evidence of disturbance of hepatic, renal, or bone-marrow activities was found in the men examined.

Discussion

The experiments described were undertaken on volunteers in London to provide information on the correct use of mepacrine in our forces campaigning in highly malarial parts of the world. It was found that a sustained mepacrine blood level of at least 100 μg per litre of blood was required to prevent malaria. Blood mepacrine levels of less than 100 μg per litre in volunteers inoculated with sporozoites invariably resulted in a real attack of malaria with parasitaemia or a transient fever without obvious parasitaemia. The transient fever was a new phenomenon which occurred in 20 out of 55 inoculated volunteers, and it obviously merited careful investigation in its relation to real attacks of malaria. It was concluded that transient fever is an early sign of an impending attack of malaria in non-immune volunteers, firstly because it invariably developed at the same time as malaria would have been expected, and secondly because malaria was transmitted on one occasion by injecting blood from an inoculated volunteer taken at the onset of transient fever. An interesting observation was made which helps to explain the self-limiting character of the transient fever. At the onset of the fever the

He was given two Codeine Phos Co tablets and slept fairly well. On the morning of the eighth day he noticed an erythematous rash on the chest and flexor aspects of the arms. He felt weak, but comfortable in bed. On the morning of the ninth day he was allowed up and walked with a perceptible limp. The rash was still present and small erythematous patches were observed on the chest and flexor aspects of the arms. On the tenth day the

TABLE VIII
*Blood Mepacrine and Severe Toxic Effects after 0.5 gm
Daily for Five Days*

Day	Blood mepacrine (μg per litre)					
	Severe toxic effects		No symptoms			
	Case I	Case G	Case C	Case K	Case Cn	Case F
5	670	480	692	288	220	206
6	1,116	1,076	787	768	558	440
7	750	—	—	—	—	—
8	—	487	228	281	618	187
9	838	—	—	—	—	—
10	—	—	—	—	—	—
11	310	214	470	230	247	164
12	224	213	197	213	262	180

Case I Severe toxic effects from days six to 10

Case G Severe toxic effects on days six and seven

rash was fading and had disappeared on the eleventh day. On the twelfth day he was able to resume duties.

Captain G During the first three days of mepacrine dosage this officer complained of epigastric discomfort, nausea, thirst, headache, and mental confusion, but was able to continue work. He was perfectly well on the fourth and fifth days. On the afternoon of the sixth day he felt weak, depressed, generally out of sorts, and had to retire to bed. Symptoms persisted on the seventh day, but on the eighth day he was well enough to resume work.

The blood mepacrine levels of the six men were estimated immediately before and 24 hours after the fifth and last doses of the drug, and again on alternate days for the next week. Twenty-four hour urinary mepacrine estimations were also made during the five days of mepacrine administration and for six days thereafter. The blood mepacrine levels of the two men who had severe reactions and the values of the other four who were unaffected are shown in Table VIII. The urinary mepacrine levels are given in Table IX. The results show that in the two patients with incapacitating toxic effects the blood-levels were higher than in the others at the time symptoms were present. No significant differences in urinary mepacrine levels were observed, so that severe systemic toxic effects seem to be directly associated with a very high level of mepacrine in the blood. A level of almost 800 μg per litre of blood 24 hours after the last dose of mepacrine was not associated with symptoms, but a level of more than 1,000 μg per litre resulted in serious toxic reactions.

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4	16.2	12.5	18.3	14.1	17.1	16.6
5	20.9	21.5	29.0	20.1	17.8	21.3
6	16.9	14.6	22.7	25.2	4.3	—
7	16.3	12.3	20.6	8.3	13.0	—
8	15.2	2.7	14.8	5.7	5.3	9.8
9	9.2	5.3	14.0	12.9	6.8	3.8
10	10.7	6.0	10.9	7.7	2.5	7.3
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Discussion

The experiments described were undertaken on volunteers in London to provide information on the correct use of mepacrine in our forces campaigning in highly malarial parts of the world. It was found that a sustained mepacrine blood level of at least 100 μg per litre of blood was required to prevent malaria. Blood mepacrine levels of less than 100 μg per litre in volunteers inoculated with sporozoites invariably resulted in a real attack of malaria with parasitaemia or a transient fever without obvious parasitaemia. The transient fever was a new phenomenon which occurred in 20 out of 55 inoculated volunteers, and it obviously merited careful investigation in its relation to real attacks of malaria. It was concluded that transient fever is an early sign of an impending attack of malaria in non-immune volunteers, firstly because it invariably developed at the same time as malaria would have been expected, and secondly because malaria was transmitted on one occasion by injecting blood from an inoculated volunteer taken at the onset of transient fever. An interesting observation was made which helps to explain the self-limiting character of the transient fever. At the onset of the fever the

blood mepacrine was below the safety level of 100 μg per litre, but at the peak it was well above this level. A reasonable inference is that the rise in blood mepacrine, induced by fever, killed the parasites and so cured the fever. How is it that the low blood-level of mepacrine at the onset of fever changes to a high level at the peak, with no additional high mepacrine dosage and indeed after mepacrine dosage has stopped? An increase in the number of leucocytes in the blood (the high concentration in leucocytes has already been referred to) has been excluded as a possible cause because exactly similar rises were observed in urinary and plasma mepacrine. The view is put forward that the change results from an alteration in the partition of the drug between tissues and blood, that the increase in the blood mepacrine level is at the expense of the large stores of the drug in the tissues, and that this results from accumulation of acid metabolites in the tissues during fever. No direct proof that this happens in the body can be provided, but support is given by *in vitro* experiments on the partition of mepacrine between protein and water. A very slight diminution in pH value in the neighbourhood of pH7 profoundly altered the partition of the drug in a simple protein-water preparation in the manner described for blood and tissues.

The incidence of transient fever in soldiers taking the routine dose of 0.1 gm mepacrine daily for malaria prevention in hyperendemic areas would be expected to be high, because about one-third of the blood mepacrine estimations in our volunteers taking this dosage were below the critical value of 100 μg per litre after the first six weeks. In our experiments 11 of 25 volunteers who actually took this dose and were inoculated with sporozoites developed transient fever. The majority of self-limiting 'pyrexias of unknown origin' that occurred in soldiers taking mepacrine in the Far East were almost certainly aborted attacks of malaria. The low blood mepacrine at the onset of transient fever in our volunteers suggest that this fever may be abolished, or its incidence greatly reduced, by increasing the daily dose of mepacrine if this is possible without causing serious toxic effects. Information on mepacrine toxicity is far from complete, but the data obtained suggest that an increase in dosage could justifiably be tried without undue risk. Serious toxic symptoms did not arise in our volunteers until the blood-level was 1,000 μg per litre or more, and as we found that dehydration precipitated alimentary symptoms from mepacrine, they may be avoided by ensuring an adequate fluid intake. It may also be of importance to ensure a liberal fluid intake during the treatment of malaria with mepacrine, because of dehydration resulting from sweating.

Another unexpected observation that led to investigation of the fate of mepacrine in the body was the fall in blood and urinary mepacrine after continuous and prolonged administration of the drug. Diminished absorption from the alimentary tract due to increased degradation of mepacrine in the bowel was considered to be the cause of this effect. Degradation of mepacrine was concluded to be the most important single factor governing the level of mepacrine in the blood, and evidence has been found which suggests

that the rates of degradation in the tissues and blood are directly proportional to one another, and also that both rates are proportional to the respective concentrations of the drug in the tissues and blood

A final point of general interest to physicians seems to emerge from the experiments reported. With oral dosage of mepacrine it was not possible to decide why some individuals developed malaria and others escaped the disease, when all were given the same amount of drug. Positive information was obtained only when a method was developed for estimating mepacrine levels in the blood. Such an approach had already been applied to the sulphonamides when our investigations began, and has since been applied to penicillin. The mepacrine experiments clearly demonstrate the practical value of this method of investigating the therapeutic value of new drugs, since by carefully controlled experiments adequate dosage for full therapeutic activity may be gauged, and the therapeutic limits defined within which toxic manifestations are avoided.

Summary

1 The chemotherapeutic action of mepacrine is directly related to the concentration of the drug in the blood. The minimal daily blood mepacrine level that will prevent malaria is about 100 μg per litre.

2 An aborted form of malaria with transient fever occurred in a considerable proportion of volunteers taking the usual suppressive dose of 0.1 gm of mepacrine daily. Parasites were not found in blood films, but frank malaria was transmitted by injection of blood into another subject. The blood mepacrine was low at the onset of the transient fever and high at its subsidence. The rise in blood mepacrine cured the fever and it is suggested that this rise is due to a transference of mepacrine to the blood from the high tissue reserves, as a result of the acidosis of fever.

3 Serious toxic reactions from mepacrine are associated with a high blood-level of the drug. The highest post-absorptive level free from ill effects is about 800 μg per litre.

4 Alimentary disturbances from mepacrine are probably due to local action of the drug. They may be prevented if liberal quantities of fluid are taken with therapeutic doses of the drug. This is of particular importance in the treatment of actual attacks of malaria, as sweating causes dehydration.

5 Degradation of mepacrine is the most important single factor that influences the level of the drug in the blood. After the drug has been taken for about two months about 70 per cent of each daily dose of 0.1 gm is degraded. The rate of degradation of mepacrine in blood has been found to be proportional to the rate of degradation in the tissues, and both rates are directly related to the respective concentrations of the drug in blood and tissues.

6 Assessment of the value of mepacrine by estimation of the blood-levels of the drug proved superior to the older practice of assessment on a dosage

basis. The merit of this approach is that it gives far more accurate information of the amount of drug which must be maintained in the blood and body fluids for full and complete therapeutic effects. Given satisfactory methods for blood estimations the method may be applicable not only for the testing of new remedies, but for improvements in the use of some that are already in use. It certainly eliminates many of the disadvantages inherent in earlier pharmacological observations, in which variability in absorption, limits of toxicity, and rate of degradation and elimination were generally unknown factors.

I wish to express my gratitude to the volunteers from the Friends' Ambulance Unit, the Pacifists' Service Unit, and the Army who made these experiments possible. I am indebted to Colonel F. S. Irvine, Commandant of the Royal Army Medical College, the Malaria Committee of the Medical Research Council, and the Board for Co-ordination of Malaria Studies in the United States of America for practical assistance throughout the work. My thanks are also due to Staff-Sergeant H. Davidson, Sergeant W. J. Park, Sergeant W. Marra, and Corporal H. A. Aubrey, all of the R. A. M. C., for invaluable technical assistance.

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A REVIEW OF CHRONIC INTERMITTENT JUVENILE JAUNDICE¹

BY E MEULENGRACHT

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Introduction

SOME years ago I described under the name chronic intermittent juvenile jaundice (*ikterus intermittens juvenilis*) a condition or disease which had previously been observed, but I considered could be conceived as a well-defined nosological entity. The disease is characterized by slight jaundice, at times distinctly visible in the skin and sclerotics, at other times present only as bilirubinaemia, accompanied by a pronounced feeling of lassitude during the periods when the jaundice is most in evidence. Otherwise there are few subjective disturbances, or none at all. The disease is observed particularly in young persons and sometimes occurs in families. It is benign in nature and gradually becomes less intense. At the present time, when attention the world over is directed towards epidemic hepatitis with its forms running a subacute or chronic course, chronic intermittent juvenile jaundice has gained a certain status, and it is important to be able to recognize this benign complaint so that confusion with the more severe subacute or chronic forms of hepatitis can be avoided. It is therefore worth while reviewing what we know about the disease at the present juncture.

History

It is undoubtedly this disease that is referred to by Gilbert and Lereboullet (1902, 1905, 1910) in the older French literature. In their investigations into haemolytic jaundice they encountered patients who exhibited a slight degree of bilirubinaemia, but lacked all the other symptoms of the disease. They employed the terms 'cholémie simple familiale' and 'cholémie physiologique' for this condition. Scheel (1911) discovered mild bilirubinaemia in a group of otherwise apparently healthy persons, and has briefly discussed this finding. Van den Bergh (1918) referred quite briefly in his book *Der Gallenfarbstoff im Blute* to the fact that one frequently meets with persons who have slight bilirubinaemia. As they appear to be healthy in every respect he called the condition 'physiologische Hyperbilirubinämie'. In his book *Die hepatohenalen Erkrankungen* Eppinger (1920) discussed Gilbert's 'cholémie simple' under the differential diagnosis of haemolytic jaundice. It is apparent that he had seen similar cases, and he seemed inclined to interpret them as mild cases of haemolytic jaundice.

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In previous investigations on haemolytic jaundice I myself have met with similar cases, and have regarded them as instances of a special disease, I have defined many of its characteristic features (Meulengracht, 1920) that it occurs chiefly in young persons, that the jaundice is apparently non-haemolytic in character, and that it persists for years, but varies in intensity and is attended by lassitude and indisposition during the more icteric periods. Weber (1917, 1931), Gänsslen, Zipperlen, and Schuz (1925), Bang (1929), and Tecon (1938) have reported briefly that they have seen similar cases. Gänsslen, Zipperlen, and Schuz interpreted the condition as 'leichte hamolytische Konstitution'. One also recognizes these patients in a publication by Diamond (1928). In routine investigations on serum-bilirubin he came across 29 young adults from 18 to 30 years of age with jaundice and various symptoms of fatigue. He classed them under the title hepatic toxæmia. In an extensive investigation on the different forms of slight and latent jaundice Rozendaal, Comfort, and Snell (1935) have also discussed the disease under the term constitutional hepatic dysfunction. By routine examination for bilirubinaemia they observed a large number of cases, the majority of which they considered belonged to this group. They are undoubtedly the same type of case that Polack (1937) and Abramson (1941) have observed, although the latter author described them as 'chronic hepatitis in young persons'.

In 1938 and 1939 I gave a full clinical description of the condition, pointing out that it was clearly a well-defined disease, characterized not only by a state of mild jaundice and fatigue, but equally by a typical and protracted course. I proposed the term 'chronic intermittent juvenile jaundice' as one which embraces the clinical picture of the complaint fairly well. Since that time the disease has been the subject of several more extensive investigations. Krarup and Roholm (1941), Welin (1945), and Alwall (1946) have made liver biopsies and examined the histological structure of the liver. Dameshek and Singer (1941), and particularly Alwall, Laurell, and Nilsby (1946), have emphasized and further investigated its occurrence in families, while various workers, specially Dameshek and Singer (1941), Welin (1945), and Alwall (1946), have made various liver function tests in a series of cases. Dameshek and Singer employed the terms 'familial, non-hemolytic jaundice' or 'constitutional hepatic dysfunction with indirect van den Bergh reaction', Alwall (1946) called the disease 'hereditary non-hemolytic bilirubinaemia without direct van den Bergh reaction'.

Material

The present paper is based on my own material and the publications of other authors. My material comprises 35 cases which I have investigated closely and followed for a number of years, that is, for one to 36 years. The patients consulted me either on their own initiative or were sent to me by their doctors for further examination, because it was noticed that they were

of subjects detected by routine examinations of the bile pigment in the blood, but of such as have been regarded as patients either by themselves or by their doctors. With respect to other authors, some have obtained their material by individual investigations of patients in the same manner as I have myself, but others have discovered them by more routine examinations for serum bilirubin (Scheel, 1911, van den Bergh, 1918, Diamond, 1928, Rozendaal, Comfort, and Snell, 1935, Vahlquist, 1939, Welin, 1945)

Symptoms

The clinical picture is fairly uniform. The symptoms consist mainly of fatigue and jaundice. There is considerable fluctuation in the condition, periods of lassitude alternating with those of less severity, and periods of jaundice with those of less intensity. Periods of lassitude and jaundice usually coincide, and the patients find it impossible to decide whether they get tired because they are jaundiced or vice versa. Some patients say that they become more jaundiced when they have good reason for being tired, for example, when they have been inebriated or have gone late to bed. The jaundice is but slight, and by direct observation is perceptible only as a yellow tinge of the sclerotics with perhaps a faint yellow coloration of the skin. As mentioned, it varies in intensity, and parallel with this the icteric index of the plasma fluctuates, the lowest I have estimated was six, the highest 36. In Table I are recorded the values of the icteric index the first time the patients came up for investigation.

TABLE I

Icteric index	5 to 10	11 to 15	16 to 20	21 to 25	26 to 30	31 to 35	36 to 40 units
	8	17	5	3	0	1	1

As an instance of the variations in a single individual the following may be cited, on December 20 Icteric index was 13, on December 27, 10, January 4, 7, January 11, 22, January 18, 10, January 25, 7, February 21, 10. Alwall, Laurell, and Nilsby (1946) gave the following variations in one of their cases within a period of three years, 36, 47, 31, 36, 16, 30, 35, 22, 42, 37, 21, 35, 12, 25, 36, 27, 18, 47, 16, 37, 12, and 21 mg per 100 cc. The values were determined by Jendrassik and Gróf's method with which Alwall, Laurell, and Nilsby found the upper normal limit to be 13 mg per 100 cc. The values may thus periodically fall within the normal limits.

On the other hand, the urine as a rule is normal in colour. It has never been possible to demonstrate bile pigment, that is, bilirubin, in it, nor, as a rule, could urobilin be detected. Thus with Marcussen and Hansen's modification of Schlesinger's test there has usually been a negative reaction, but sometimes a very weak positive reaction, and occasionally a more distinct one, but in reality it does not deviate greatly from what is found under normal conditions. The same finding has been reported by van den Bergh (1918) and Dameshek and Singer (1941), but Bang (1929),

In previous investigations on haemolytic jaundice I myself have met with similar cases, and have regarded them as instances of a special disease, I have defined many of its characteristic features (Meulengracht, 1920) that it occurs chiefly in young persons, that the jaundice is apparently non-haemolytic in character, and that it persists for years, but varies in intensity and is attended by lassitude and indisposition during the more icteric periods Weber (1917, 1931), Gänsslen, Zipperlen, and Schuz (1925), Bang (1929), and Tecon (1938) have reported briefly that they have seen similar cases Gänsslen, Zipperlen, and Schuz interpreted the condition as 'leichte hämolytische Konstitution' One also recognizes these patients in a publication by Diamond (1928) In routine investigations on serum-bilirubin he came across 29 young adults from 18 to 30 years of age with jaundice and various symptoms of fatigue He classed them under the title hepatic toxæmia In an extensive investigation on the different forms of slight and latent jaundice Rozendaal, Comfort, and Snell (1935) have also discussed the disease under the term constitutional hepatic dysfunction By routine examination for bilirubinaemia they observed a large number of cases, the majority of which they considered belonged to this group They are undoubtedly the same type of case that Polack (1937) and Abramson (1941) have observed, although the latter author described them as 'chronic hepatitis in young persons'

In 1938 and 1939 I gave a full clinical description of the condition, pointing out that it was clearly a well-defined disease, characterized not only by a state of mild jaundice and fatigue, but equally by a typical and protracted course I proposed the term 'chronic intermittent juvenile jaundice' as one which embraces the clinical picture of the complaint fairly well Since that time the disease has been the subject of several more extensive investigations Krarup and Roholm (1941), Wehn (1945), and Alwall (1946) have made liver biopsies and examined the histological structure of the liver Dameshek and Singer (1941), and particularly Alwall, Laurell, and Nilsby (1946), have emphasized and further investigated its occurrence in families, while various workers, specially Dameshek and Singer (1941), Wehn (1945), and Alwall (1946), have made various liver function tests in a series of cases Dameshek and Singer employed the terms 'familial, non-hemolytic jaundice' or 'constitutional hepatic dysfunction with indirect van den Bergh reaction', Alwall (1946) called the disease 'hereditary non-hemolytic bilirubinaemia without direct van den Bergh reaction'

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practically restricted to jaundice and lassitude. A number of authors (Gilbert, Lereboullet, and Herscher, 1907, Tecon, 1938, Dameshek and Singer, 1941, Wehn, 1945, Alwall, 1946) assert, however, that gastrointestinal disturbances are a frequent finding—'obstipation', 'entérite mucomembranense', 'dyspepsie hyperpéptique', 'langsame Verdauung oder mehr oder minder ausgeprägte dyspeptische Störungen und unregelmässiger Stuhlgang', 'stomach disorder', 'dyspeptic disorder', 'dyspeptic troubles and diarrhoea', 'diffuse stomach disorder', 'slight colitis troubles', 'unkarakteristische Dyspepsie', &c, so there must clearly be some truth in it. Two of my patients said that they sometimes had pain at the right costal margin.

The Negative Findings

No abnormality of the internal organs has ever been found by physical examination. In particular, no enlargement of the spleen could be detected by physical or radiological examination (Wehn, 1945). All authors are in agreement about this. The blood has naturally been examined by practically all authors. Anaemia has never been demonstrated, the osmotic resistance of the red cells was normal, there was no microcytosis nor spherocytosis, and the reticulocytes were not increased in number. The most thorough investigations were carried out by Dameshek and Singer (1941). They also undertook biopsies of the bone-marrow, which they found to be normal. Further, they made quantitative examinations of the urobilin excretion in the faeces as a measure of blood destruction, and found normal or low values.

Liver function tests have been done fairly extensively. The van den Bergh reaction was negative, direct, or delayed, direct (van den Bergh, 1918, Dameshek and Singer, 1941, Wehn, 1945, Alwall, 1946). The galactose test was negative (Meulengracht, 1939, Alwall, 1946) or in a few cases weakly positive (Wehn, 1945). The hippuric acid test was negative or in a few cases weakly positive (Wehn, 1945, Alwall, 1946). The citric acid values of the blood were slightly increased in a good many cases (Wehn, 1945, Alwall, 1946). The power of excreting bilirubin was found to be depressed by the concentration test (Dameshek and Singer, 1941, Wehn, 1945), but the Takata reaction was always negative (Meulengracht, 1939, Wehn, 1945, Alwall, 1946). In those 10 cases in which I have tested it the blood sedimentation was normal, the highest figure being 6 mm in one hour.

Liver biopsy, by the method introduced by Iversen and Roholm in 1939, was undertaken by Krarup and Roholm (1941) in five cases. In three a normal histological picture was present, while in two there was slight fatty infiltration of the liver cells. Changes of the kind that occur in chronic hepatitis were not found. Wehn (1945) made a liver biopsy in six cases. In three there was a slight fatty infiltration of the liver cells. Inflammatory changes or signs of cirrhosis were not observed. The above findings were confirmed by Alwall (1946) in two cases and in one of my cases.

Diamond (1928), Polack (1937), and Alwall (1946) claimed to have found urobilinogen in a number of their cases. In no case has itching of the skin been present. It may therefore be said that the jaundice is characterized by a slight degree of bilirubinaemia, varying in intensity.

In my opinion the periodic lassitude is just as characteristic a factor as jaundice, perhaps more so. It is described as being both bodily and mental in nature, but it seems specially to form a check on concentrated mental work, phrases such as these are used to describe it—'tired and no energy', 'quickly tired out after mental work', 'find it difficult to concentrate while reading', 'lack of initiative', 'doesn't make the daily routine work more arduous, but robs me of that little extra energy and initiative which makes work a pleasure'. One patient said that he was so tired in the morning that he got sensations of nausea and extreme weakness in the back. Several others also mention a tendency to nausea. Some state that they become irritable. Patients cite the following as direct causes of the bad periods—spirits ('but the worst is spirits', 'most marked next day', 'can't stand beer or spirits'), insufficient sleep ('need eight hours' sleep', 'a night out'), overwork, grief and worry (divorce), anger, stomach troubles and other intercurrent symptoms, the early spring. On the other hand, two women volunteered the information that 'it entirely disappeared during pregnancy' and 'while I was pregnant I bore no trace of a yellow colour and felt very fit'. The periods are subject to varying frequency. One of my patients, a young doctor, said that his periods of fatigue lasted five, 10, 20, or 30 days and his free periods about the same time, but that he had once had an entirely free period for four to five years.

Diamond (1928), whose cases I have no doubt are of the same nature, gives the following subjective symptoms—general indisposition, fatiguability, loss of ambition, nervousness, irritability, depression, and digestive disturbances. Abramson (1941), whose cases without doubt also fall into the same category, emphasized the lassitude which prevented the patients, who were engaged in hard manual labour, from doing their work. Other authors who have had individual cases under observation for a long time also lay stress on the lassitude, but there are some authors who state that patients suffering from slight bilirubinaemia are subjectively healthy and free from symptoms. There is a fundamental difference involved here according to whether patients with bilirubinaemia consult their doctors for jaundice and fatigue, or whether they are encountered in a routine examination for bilirubinaemia. Those authors whose material is mainly derived from such routine investigations seem more inclined to stress freedom from symptoms, as one would expect.

On questioning, some patients have admitted mild dyspeptic attacks or intestinal disturbances, while one had typical fermentation colitis, but I have formed the impression that these symptoms do not amount to more than might be met with in a control group followed for a long time. Therefore I still believe, from my own experience, that the symptoms are

practically restricted to jaundice and lassitude. A number of authors (Gilbert, Lereboullet, and Herscher, 1907, Tecon, 1938, Dameshek and Singer, 1941, Welin, 1945, Alwall, 1946) assert, however, that gastrointestinal disturbances are a frequent finding—'obstipation', 'entérite mucomembraneuse', 'dyspepsie hyperpéptique', 'langsame Verdauung oder mehr oder minder ausgeprägte dyspeptische Störungen und unregelmässiger Stuhlgang', 'stomach disorder', 'dyspeptic disorder', 'dyspeptic troubles and diarrhoea', 'diffuse stomach disorder', 'slight colitis troubles', 'unkarakteristische Dyspepsie', &c, so there must clearly be some truth in it. Two of my patients said that they sometimes had pain at the right costal margin.

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Welin (1945) found the basal metabolic rate diminished in some cases, but Alwall (1946) reported it sometimes to be slightly raised. The aneurin content of the serum was found by Welin (1945) to be decreased in some cases.

Incidence

The clinical picture described above is observed in young persons, and apparently rather more frequently in men. Among my 35 cases, 23 were men and 12 women. The apparent excess of men is due partly to the fact that for special reasons the series included eight medical students or doctors. The cases varied in age from 14 to 34 years, and were distributed according to Table II.

TABLE II

Age	15 to 20	21 to 25	26 to 30	31 to 35 years
Number of cases	9	16	7	3

The figures in the Table do not mean that the symptoms began or first appeared at the ages indicated, but merely signify the age when the patients first consulted me. Yet a large number of them already had had symptoms of many years' standing. It was very difficult to obtain a true account of the age at which the symptoms actually started. Frequently they had become aware of their condition from the chance remarks of friends. Consequently they did not know whether they had been slightly jaundiced beforehand. In one instance it was stated that jaundice had been noticed at the age of 12 years. Alwall's (1946) material comprised 11 men and four women from 19 to 40 years of age. His patients asserted that they had been jaundiced for years, some saying 'since childhood' or 'always'. Abramson's (1941) total of 10 patients were all men. As mentioned, there were a number of medical students and young doctors among my cases. Bang (1929) and Polack (1937) had the same experience (Bang, four out of six, Polack, five out of eight), but presumably the reason for this is that the condition is more readily recognized either by the patients themselves or by their attention being drawn to it by their fellow students, so that they came up to be examined. Since the disease is hardly likely to be more frequent among the medical profession than among the laity, it may perhaps be concluded from these findings that the condition must be fairly common. On the whole, academic persons and educated people are represented remarkably frequently in my material, whereas the working class are not. The explanation may be that the latter do not consult a doctor for the disease, at least not me, but perhaps also because the spells of fatigue seem specially to interfere with mental work. Abramson's (1941) patients, significantly from a country hospital, were, however, 'all but one engaged in hard manual labour'.

The problem of the frequency of occurrence of the disease is one towards which it is very difficult to take up a definite attitude. If an estimate is made on the basis of the number of patients who come to a doctor complaining of jaundice or lassitude the numbers are relatively small, but if account

is taken of the number of persons who on routine examination of the serum-bilirubin show values which would be regarded as increased, the total becomes large

Fairly numerous investigations of the serum-bilirubin in apparently healthy persons are available. On inspection of the values of Vaughan and Hasle-

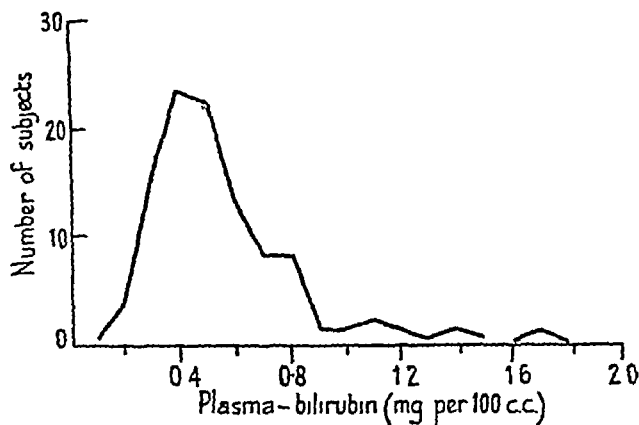


FIG 1 Frequency distribution of plasma-bilirubin in 100 healthy adults (Vaughan and Haslewood, 1938)

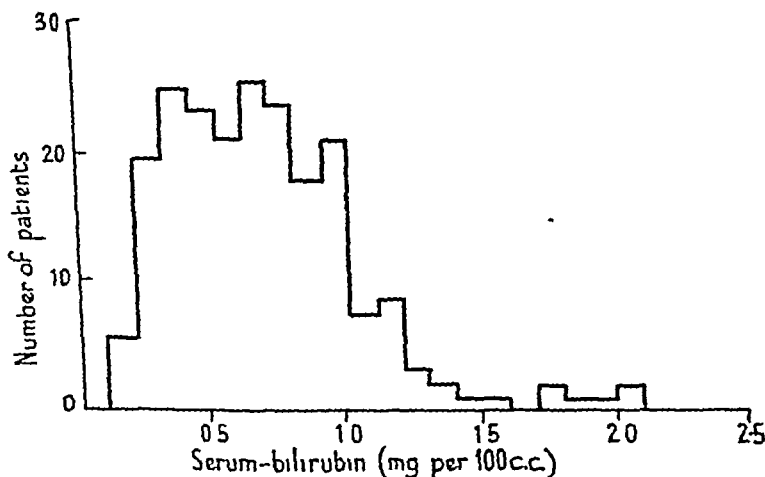


FIG 2 Distribution of the serum-bilirubin in 200 medical patients (With, 1943)

wood (1938), With (1943), and Alwall, Laurell, and Nilsby (1946) it will be observed that they all have the same distribution curve, which rises obliquely, in that there are a number of estimations which are high and appear to fall outside it

Vaughan and Haslewood were content to say that they 'would suggest that, for the present, figures between 0 and 1.3 mg per 100 c.c. should be

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Age	15 to 20	21 to 25	26 to 30	31 to 35 years
Number of cases	9	16	7	3

The figures in the Table do not mean that the symptoms began or first appeared at the ages indicated, but merely signify the age when the patients first consulted me. Yet a large number of them already had had symptoms of many years' standing. It was very difficult to obtain a true account of the age at which the symptoms actually started. Frequently they had become aware of their condition from the chance remarks of friends. Consequently they did not know whether they had been slightly jaundiced beforehand. In one instance it was stated that jaundice had been noticed at the age of 12 years. Alwall's (1946) material comprised 11 men and four women from 19 to 40 years of age. His patients asserted that they had been jaundiced for years, some saying 'since childhood' or 'always'. Abramson's (1941) total of 10 patients were all men. As mentioned, there were a number of medical students and young doctors among my cases. Bang (1929) and Polack (1937) had the same experience (Bang, four out of six, Polack, five out of eight), but presumably the reason for this is that the condition is more readily recognized either by the patients themselves or by their attention being drawn to it by their fellow students, so that they came up to be examined. Since the disease is hardly likely to be more frequent among the medical profession than among the laity, it may perhaps be concluded from these findings that the condition must be fairly common. On the whole, academic persons and educated people are represented remarkably frequently in my material, whereas the working class are not. The explanation may be that the latter do not consult a doctor for the disease, at least not me, but perhaps also because the spells of fatigue seem specially to interfere with mental work. Abramson's (1941) patients, significantly from a country hospital, were, however, 'all but one engaged in hard manual labour'.

The problem of the frequency of occurrence of the disease is one towards which it is very difficult to take up a definite attitude. If an estimate is made on the basis of the number of patients who come to a doctor complaining of jaundice or lassitude the numbers are relatively small, but if account

is taken of the number of persons who on routine examination of the serum-bilirubin show values which would be regarded as increased, the total becomes large

Fairly numerous investigations of the serum-bilirubin in apparently healthy persons are available. On inspection of the values of Vaughan and Hasle-

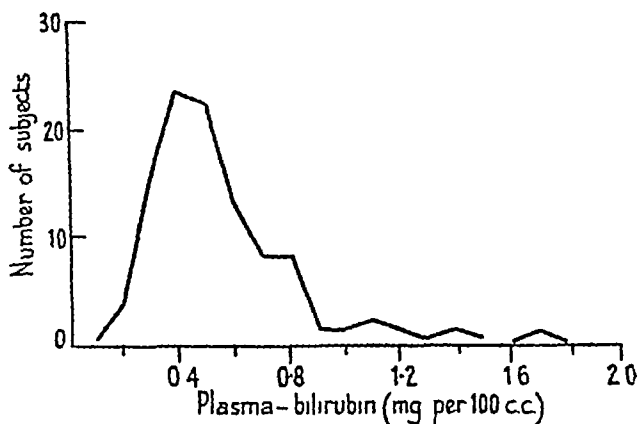


FIG 1 Frequency distribution of plasma bilirubin in 100 healthy adults (Vaughan and Haslewood, 1938)

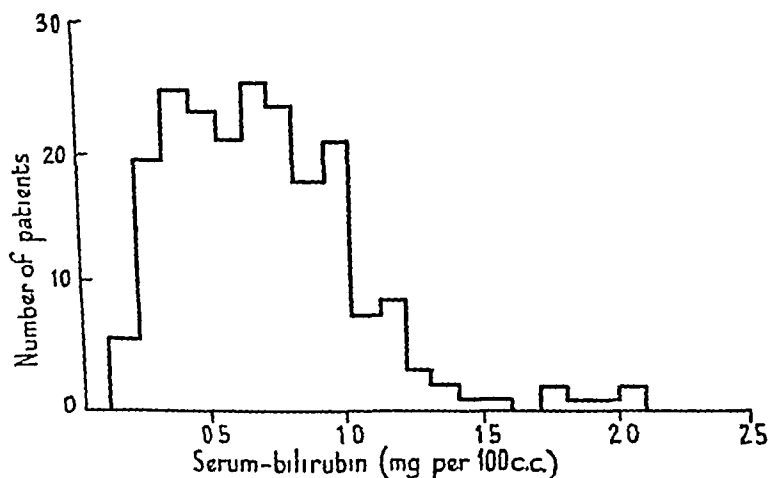


FIG 2 Distribution of the serum bilirubin in 200 medical patients (With, 1943)

wood (1938), With (1943), and Alwall, Laurell, and Nilsby (1946) it will be observed that they all have the same distribution curve, which rises obliquely, in that there are a number of estimations which are high and appear to fall outside it

Vaughan and Haslewood were content to say that they 'would suggest that, for the present, figures between 0 and 1.3 mg per 100 c.c. should be

Welin (1945) found the basal metabolic rate diminished in some cases, but Alwall (1946) reported it sometimes to be slightly raised. The aneurin content of the serum was found by Welin (1945) to be decreased in some cases.

Incidence

The clinical picture described above is observed in young persons, and apparently rather more frequently in men. Among my 35 cases, 23 were men and 12 women. The apparent excess of men is due partly to the fact that for special reasons the series included eight medical students or doctors. The cases varied in age from 14 to 34 years, and were distributed according to Table II.

TABLE II

Age	15 to 20	21 to 25	26 to 30	31 to 35 years
Number of cases	9	16	7	3

The figures in the Table do not mean that the symptoms began or first appeared at the ages indicated, but merely signify the age when the patients first consulted me. Yet a large number of them already had had symptoms of many years' standing. It was very difficult to obtain a true account of the age at which the symptoms actually started. Frequently they had become aware of their condition from the chance remarks of friends. Consequently they did not know whether they had been slightly jaundiced beforehand. In one instance it was stated that jaundice had been noticed at the age of 12 years. Alwall's (1946) material comprised 11 men and four women from 19 to 40 years of age. His patients asserted that they had been jaundiced for years, some saying 'since childhood' or 'always'. Abramson's (1941) total of 10 patients were all men. As mentioned, there were a number of medical students and young doctors among my cases. Bang (1929) and Polack (1937) had the same experience (Bang, four out of six, Polack, five out of eight), but presumably the reason for this is that the condition is more readily recognized either by the patients themselves or by their attention being drawn to it by their fellow students, so that they came up to be examined. Since the disease is hardly likely to be more frequent among the medical profession than among the laity, it may perhaps be concluded from these findings that the condition must be fairly common. On the whole, academic persons and educated people are represented remarkably frequently in my material, whereas the working class are not. The explanation may be that the latter do not consult a doctor for the disease, at least not me, but perhaps also because the spells of fatigue seem specially to interfere with mental work. Abramson's (1941) patients, significantly from a country hospital, were, however, 'all but one engaged in hard manual labour'.

The problem of the frequency of occurrence of the disease is one towards which it is very difficult to take up a definite attitude. If an estimate is made on the basis of the number of patients who come to a doctor complaining of jaundice or lassitude the numbers are relatively small, but if account

(1935) patients it was stated that the jaundice first appeared at birth or after birth. Some of Alwall's (1946) patients are said to have had jaundice since childhood or always. These assertions are to some extent open to doubt. The fact is that the disease, jaundice and periods of lassitude, is usually first noticed between the ages of 15 and 25 years, but it can well be assumed that the symptoms have been present, although undetected, for

TABLE III

Case number	Sex	Date when first seen by author	Age when jaundice first noticed (years)	Present age (years) (in 1943)	Length of observation (years)
1	F	1917	<25	51	26
2	M	1917	<21	46	25
3	M	1919	<24	57	27
4	F	1924	14	Died in 1926	—
5	F	1925	<15		>18
6	M	1925	14		20
7	M	1926	20		24
8	M	1927	15	32	17
9	M	1927	<22	37	15
10	F	1927	19	45	26
11	M	1930	17	36	19
12	M	1931	17	35	18
13	M	1932	17	34	17
14	M	1933	14	34	20
15	M	1934	21	30	9
16	M	1934	17	36	19
17	M	1934	22	31	9
18	M	1934	<34	43	>9
19	M	1935	16	24	8
20	F	1936	14	25	7
21	M	1936	<23	30	>7
22	F	1936	<20	27	>7
23	F	1936	16	29	13
24	F	1938	31	37	6
25	M	1939	21	25	4
26	F	1939	23	32	9
27	M	1939	15	21	6
28	M	1941	19	30	11
29	M	1943	15	26	11

some time previously. That the disease becomes most evident clinically between 15 and 25 years of age seems to be undeniable. It is during this period that the doctor gets in touch with the patients. When they reach a greater age the doctor apparently loses contact with them, either because the symptoms are not so prominent or because the patients have become accustomed to them. That the symptoms gradually become less marked is indicated by an after-investigation which I undertook in 1944. I was successful in collecting information about all the patients (29) that I had treated up to that date for chronic intermittent juvenile jaundice. I obtained full details about them all, some of them I saw personally and re-examined. The observation periods extended from four to 27 years.

From the patients' own accounts and from other information which could be obtained, it emerged that none of them had experienced any aggravation of the condition and nothing had supervened which could be regarded as

considered as probably normal' With (1943) interpreted the high values in his normal material as physiological (physiological bilirubinaemia), and considered it unlikely that cases of chronic intermittent juvenile jaundice are included, at any rate in significant numbers Alwall, Laurell, and Nilsby (1946) stated that their normal material might include mild patho-

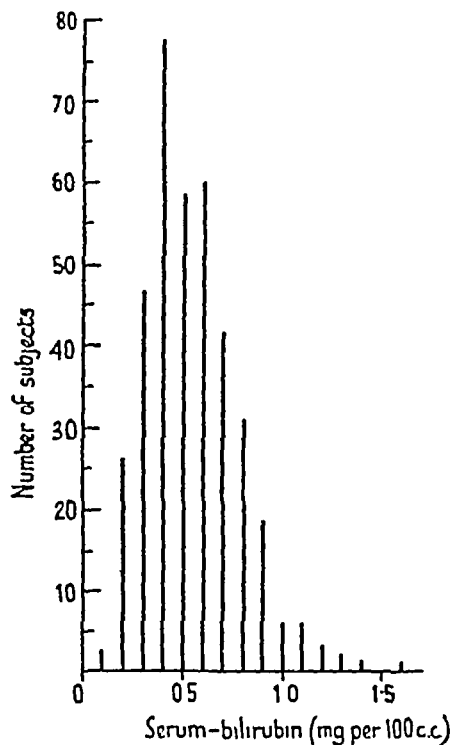


FIG 3 The bilirubin content in serum, determined according to Jendrassik and Gróf, among 383 subjectively healthy subjects, 263 men and 120 women (Alwall, Laurell, and Nilsby, 1946)

logical cases, including chronic intermittent juvenile jaundice, and that normal figures obtained from such normal material are unreliable and directly misleading. As a practical working hypothesis they proposed 1.3 mg per 100 c.c. as the upper limit for normal serum-bilirubin values. It will be seen that the same difficulties are cropping up again, what is to be done with the high values? Elton (1935, 1936) (cited by Vaughan and Haslewood, 1938), who apparently also made determinations in presumably healthy subjects, interpreted the high values as cases of 'familial jaundice' and claims that familial jaundice is met with in approximately 3 per cent of the white races, being specially prevalent in Jews, but this is clearly only overcoming the difficulty by a postulate.

My own view is that the problem of the significance of high serum-bilirubin values in normal material should remain open for the time

being. It can be decided only by following the subjects for a long period of time in order to see what happens to them. In no other way can be brought to light what is behind these high values, and how many of the subjects can be classed as cases of chronic intermittent juvenile jaundice. Special weight must be attached to the chronic intermittent course of the disease and the periods of lassitude, but in a close follow-up of individuals with high serum-bilirubin values it must be constantly kept in mind that latent jaundice or sub-jaundice is a very common attendant phenomenon in a host of morbid conditions.

Course and Prognosis

It is difficult to obtain information about the time when the condition or disease commences. In the case of some of Rozendaal, Comfort, and Snell's

been discussed by Gilbert, Lereboullet, and Herscher (1907), van den Bergh (1918), Tecon (1938), Rozendaal, Comfort, and Snell (1935), Vahlquist (1939, 1941), and Welin (1945). The usual finding has been that in some instances the condition has been observed in several brothers and sisters, perhaps in one of the parents, but the inquiry has been left at that. I myself have made similar observations, thus I have included three brothers and sisters in my material, and in three other cases I obtained information that one or more brothers and sisters had similar symptoms, but I have omitted questioning my patients thoroughly on this matter and have not undertaken further family investigations. Dameshek and Singer (1941) found the condition present in two brothers of one family, and in the father and seven out of eight brothers and sisters of another. They assumed that the condition is predominantly hereditary. More systematic investigations on heredity were undertaken by Alwall, Laurell, and Nilsby (1946), through which interesting observations have been brought to light. They made systematic determinations of the serum-bilirubin in the relations of 15 patients. In 65 brothers and sisters of these 15 patients they discovered increased values in 55 per cent, in 19 parents increased values in 26 per cent, while in 35 more distant relations the values were increased in 6 per cent. By increased values they understood those which were over 1.3 mg per 100 cc of bilirubin estimated by Jendrassik and Gróf's method, this value they had found to be the upper limit for the normal in a large number of subjectively healthy people. The bilirubin level in general was lower among the healthy relatives than among the patients, and the relatives with bilirubinaemia were subjectively in good health. Renewed control, however, in some of these cases brought about a period of fatigue and uneasiness. Some of the families were investigated genealogically, but the authors found no evidence that it was a simple dominant character, and they therefore let the problem of the hereditary process remain an open question. They wrote 'only a greater material under lengthier observation can be expected to give an answer to this question', but even with simple dominance prevailing one would expect an indistinct picture on account perhaps of incomplete dominance, variations in the condition with temporarily absent bilirubinaemia and the possibility of the condition fading out in the older age-groups. The hereditary process is not the vital factor. The chief point is that the disease possesses a hereditary basis, which clearly manifests itself with considerable frequency when it is looked for carefully.

Aetiology

It will appear from what has been said above that the hereditary basis of the disease is evident, so that the cause must be sought for at least partly in genotypical factors, but a series of external incidental factors act on this hereditary foundation which induce or aggravate the condition. To these belong, according to the patients' statements, alcohol, convivial evenings, lack of sleep, sorrow and anxiety, and overwork, as previously mentioned.

a sign that chronic hepatitis or any other serious disease existed. On the other hand, it appeared that as the years passed by an improvement in the condition had usually taken place. It was as if the whole clinical picture had faded somewhat, that is to say, the sub-icteric periods and the feeling of fatigue were less pronounced, but the symptoms persisted to a more advanced age than I had originally thought to be the case, some of them were by then in their forties and could still detect their symptoms which may indeed last still longer in some of the cases. Here are a couple of patients' answers by way of illustration.

A N 44 years Doctor 'Have not been treated since for the jaundice. It is not present continuously, and I think that it has definitely occurred at longer intervals in later years. I have the impression that it appears particularly at times when I have much to do, while it is generally absent during holidays. But I must admit that my interest in watching the symptoms has flagged considerably in the course of years. The last time that the jaundice was distinct enough for my friends to remark upon it was last summer when it was associated with an attack of diarrhoea.'

K A 37 years Doctor 'On the whole I have felt well since 1927, at any rate I can definitely say that I have not reported sick a single day on account of my jaundice condition. Spells of lassitude still continue, but I am convinced that compared with 10 years ago the feeling of tiredness has considerably diminished. Long periods may elapse in which I feel nothing and have really completely forgotten that there has ever been anything wrong with me. The yellow colour also is always present, but it is rather variable. I personally believe it is decreasing and I do not think I have such yellow periods as formerly, but it happens constantly that my colleagues exclaim "But you really are jaundiced." Going to bed late has a bad effect on me, I need eight hours' sleep. But the worst thing is spirits which has a direct depressing action for the next few days. But if I avoid these evils I consider my capacity for work is on the same level as that of others.'

The result of the after-investigation, however, is to confirm the impression originally gained of the absolutely benign nature of the disease or condition, while the conception of the prognosis remains unchanged, even though the material includes an isolated case in which the diagnosis is open to doubt.

Rozendaal, Comfort, and Snell (1935), whose starting-point was evidently the routine laboratory examination for serum-bilirubin, reported that in 29 per cent of their patients who had jaundice of the constitutional type, disease of the gall-bladder eventually developed, and they concluded that this implies that constitutional hepatic dysfunction, at least of the grade capable of producing jaundice, predisposes to disease of the gall-bladder. In view of my follow-up investigation I am quite unable to appreciate this, and, moreover, it figures as a unique statement. As pointed out by Alwall (1946), the good prognosis is significant from the point of view of life insurance.

Hereditry

Hereditary occurrence can be traced in some of the cases, and the more attention is directed to it the more frequently will it be recognized. It has

which indicate a common infection. As regards some of the cases, it is stated that the condition began originally with 'jaundice', that is to say, it was thus called when it was first noticed, but in none of my cases have there ever been symptoms which were different from, or more severe than, what I subsequently observed. There has not been more pronounced jaundice, no acholic type of faeces, and no dark urine. The same applies to Polack's (1937) and Abramson's (1941) cases, which in fact are interpreted as chronic hepatitis, thus it is said that they developed after attacks of acute hepatitis which, however, were manifest only as 'extremely weak phenomena'.

Certain liver function tests detect a trifling depreciation of the liver function, such as the citric acid test and the bilirubin elimination test after a dose of this substance, but it is neither different from, nor more than, is already expressed by the very fact that there is slight jaundice. The most important of the liver function tests, the Takata reaction, is always negative. This is significant because a positive result of this reaction is so characteristic of subacute or chronic hepatitis. Krarup and Roholm (1941) showed by numerous liver biopsies that a positive Takata reaction consistently develops *pari passu* with the chronic interstitial changes in the liver during the course of the hepatitis, and at the present time when subacute and chronic epidemic hepatitis occurs in this country with extreme frequency (Bjørneboe and Brøchner-Mortensen, 1945, Jersild, 1945, Alsted, 1946), we know that a positive Takata reaction is one of the surest criteria for the diagnosis of subacute and chronic hepatitis. Then finally, and most important of all, there are the liver biopsy results (Krarup and Roholm, 1941, Wehn, 1945, Alwall, 1946, Meulengracht, 1938). They one and all show that in chronic intermittent juvenile jaundice there are no inflammatory changes in the liver whatever, cellular or interstitial. It may therefore be regarded that slight chronic hepatitis is excluded as the basis of the condition.

For the present it may be said that the pathogenesis is unknown. It must be remarked that it is far from certain that the primary seat is in the liver. The liver is a sensitive organ which reacts with slight jaundice to many different influences, and the starting-point of the complaint may be in other places than this organ. To mention only one example, it has been demonstrated (Hetényi, 1923, Hunt, 1933, McClure and Huntsinger, 1927, Diamond, 1928) that during a migraine attack slight bilirubinaemia occurs, without its being claimed that the seat of the trouble is in the liver. To my mind there is nothing preposterous in seeking the origin of chronic intermittent juvenile jaundice with its principal symptoms of fatigue and bilirubinaemia in some site in the organism other than the liver.

Diagnosis

As a matter of course it must be borne in mind, in dealing with the individual case, that jaundice is of extremely common occurrence and that many different conditions can produce it, but first of all chronic hereditary

Perhaps the gastro-intestinal disturbances which some authors lay stress on should be put in this class and regarded as provocative factors

Pathogenesis

The first question is whether to regard the condition as physiological, that is to say, as falling within the natural limits of variation, or as a deviation from the normal. Even if the bilirubin values at times may fall within the normal boundaries, it seems to be excluded that the entire condition can be so regarded. The cases figure as a group distinct from the normal, amongst other things by the presence of a subjective symptom of a definite pathological nature, namely, fatigue. Another explanation must therefore undoubtedly be looked for.

To a casual observer the condition may suggest chronic hereditary haemolytic jaundice. There is the same slight degree of jaundice as in this disease and a similar varying intensity, but it can straightway be established that the complaint has nothing to do with this disease and that the jaundice is not haemolytic in type, since all the symptoms of increased haemolysis are lacking. There is no splenic enlargement, no anaemia, no diminished osmotic resistance of the red cells, no microcytosis or spherocytosis, and no reticulocytosis. These points have been thoroughly investigated with perfectly uniform results. The quantitative urobilin excretion in the faeces was found to be below normal (Dameshek and Singer, 1941, Alwall, 1946). The bone-marrow was normal (Dameshek and Singer, 1941). Thus investigations on these latter points also do not favour the existence of increased haemolysis and blood regeneration. Although earlier authors have advanced the possibility that it might be a question of 'leichte hämolytische Konstitution', by which, no doubt, cases of chronic hereditary jaundice with few symptoms is meant, we can now refute this view. That the van den Bergh reaction, direct or delayed direct, is negative is, in this connexion, beside the point. It was long ago established, both by van den Bergh himself and by many others, that a negative direct or delayed direct reaction occurs in other forms of mild or chronic jaundice as well as in haemolytic jaundice, even indeed in the protracted jaundice following hepatitis.

The next point is whether the condition is due to mild chronic hepatitis. It is known that slight bilirubinaemia can persist for some time after acute epidemic hepatitis, varying in intensity, but sometimes strong enough to induce a trace of sub-jaundice. Here it is a question of a protracted convalescent stage, a kind of residual bilirubinaemia. It is likewise recognized that acute epidemic hepatitis passes into subacute or chronic hepatitis in a certain number of cases. It is possible that such cases lie hidden in the different material, which in reality are subacute and chronic hepatitis, but this affords no satisfactory explanation of the bulk of the cases. The hereditary character of the condition does not seem to be in harmony with its being subacute or chronic hepatitis, and there are no observations extant

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haemolytic jaundice and epidemic hepatitis in its subacute and chronic forms must be excluded. It is easy enough to exclude the first disease. All the typical symptoms, enlargement of the spleen, diminished osmotic resistance, spherocytosis, reticulocytosis, and hyperphasia of the red bone-marrow, are wanting in chronic intermittent juvenile jaundice. It is unnecessary to deal with this case any further. It should also be possible to exclude epidemic hepatitis in both its subacute and chronic forms, although in this case it may be rather more difficult. In favour of intermittent juvenile jaundice is the absence of previous acute hepatitis, scarcely visible jaundice, no urobilinuria, a normal sedimentation rate, and a negative Takata reaction. In favour of subacute or chronic hepatitis there is a greater degree of jaundice, periods of increased urobilinuria, possibly periods of bilirubinuria, a positive Takata reaction, an increased sedimentation rate, general deterioration, foetor hepaticus, and stellate telangiectases of the skin (spider telangiectases). If, in spite of all this, a satisfactory decision cannot be reached, as a last resort liver biopsy will settle the question. In addition there is the tangible fact to rely on, namely, that young adults with hardly visible jaundice, varying in intensity but spread over years, and pronounced periods of fatigue, provide a typical and easily recognizable picture.

Treatment

As has been stated, a number of external factors such as indulgence in alcohol, lack of sleep, overwork, excitement, intercurrent diseases, &c, have a certain amount of influence on the condition and aggravate the symptoms, but beyond avoiding such harmful effects and pursuing an orderly way of life in dietetic and hygienic matters it can safely be said that we possess no specific therapy. I have tried arsenic, various vitamins, &c, without being able to produce any result. The most important therapy one can give patients is a diagnosis. This is of value because the condition, as mentioned, can give rise to anxiety from which it is beneficial to be able to free the patient. This is well illustrated by a couple of replies—'I always remember with gratitude that you then banished the fear that I was suffering from chronic hepatitis', and 'I am now convinced that it is a benign disease or anomaly which it is not worth while bothering about. Nor have I ever consulted anyone else about my disease, in fact I have ignored it entirely.'

Nomenclature

As will appear from the above, the condition discussed here has been described under various headings. Both from a nosographical and a purely practical standpoint it is by no means a matter of indifference under what title a morbid condition is admitted into the nosographical system. In the first place the title must not be inaccurate such as 'hämolytische Konstitution' and 'chronic hepatitis in young persons' may be said to be. Nor must it be too comprehensive, an objection which can well be levelled at the

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FAT ABSORPTION IN TROPICAL SPRUE¹

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SINCE impairment in fat absorption, as shown by the excretion of fatty stools, is the most constant and characteristic feature of the sprue syndrome, an investigation on sprue should be based on adequate methods of measuring fat absorption. Simple estimation of the percentage of fat in the dry stool, although it may be of some use in diagnosis, does not give quantitative information on the amount of fat actually absorbed, for it takes no account of the amount of fat in the diet, nor does it measure the total excretion of fat over any known period. When a patient with sprue is put on a controlled diet of known fat content, and all the stools for a definite period are collected, weighed, and analysed, it becomes possible to relate fat intake to fat output, the percentage of fat absorbed over the period in question is given by the expression

$$\left(\frac{(\text{dietary fat} - \text{faecal fat})}{\text{dietary fat}} \times 100 \right)$$

Fat-balance studies of this kind have been made in idiopathic steatorrhoea by Bassett, Kentmann, Hyde, Van Alstine, and Russ (1939), but we have not been able to find any record of the application of this method to tropical sprue. The object of the work described in the present paper was to assess the severity of the fat absorption defect in tropical sprue, and to find out whether fat absorption could be improved by nicotinic acid and riboflavine, or by liver and yeast extract. A preliminary communication (Black, Fourman, and Trinder, 1946) has outlined some of the conclusions reached, but the evidence on which they are based has not yet been fully presented.

Material

The 28 patients studied were all soldiers who had acquired sprue on tropical service in India or South-East Asia Command. All of them had steatorrhoea, and had lost 10 per cent or more of their body-weight, glossitis, moderate anaemia, and abdominal distension were common. Many patients with sprue, when admitted to hospital and put on a controlled diet of moderate fat content, show spontaneous improvement. Patients who were obviously improving rapidly at the time of admission have been excluded, patients who were not showing signs of improvement were put on a controlled diet, and their stools collected. An interval of from eight to 24 days was

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allowed to pass before any specific treatment was begun. Five patients whose condition permitted it were observed throughout without specific treatment, the other 23 patients were treated in various ways, as described below. The usual period of observation for each patient was six weeks to two months.

Methods

Two standard diets were used, one with 65 to 70 gm of fat per diem, the other with 95 to 100 gm of fat. Those patients who could tolerate the diet of higher fat content were put on it at the beginning of the observation period, others began on the 65 to 70 gm diet, and most, but not all, of these were transferred to the higher diet as they improved. The diet was weighed out in the ward kitchen, and food residues were also weighed. The fat content of the diet was calculated from food tables (McCance and Widdowson, 1939), and the main sources of fat were analysed at intervals to ensure that they conformed to the values given in the tables for English foodstuffs. Variations in appetite led to deviation from the planned fat content of the diet in some cases, but the appropriate corrections based on the amount of food left over have been made in calculating the percentage fat absorption for each period. The total stools for three- or four-day periods were collected in large tin vessels and preserved with formalin. Carmine and iron markers were used to demarcate the periods. The stools were weighed and thoroughly mixed with a large ladle. Samples of 20 to 50 gm were transferred to weighed Petri dishes, and air-dried on a warm surface under a fan, the wet and dry weights of the sample were determined. One-gram samples of the dried stool were extracted thrice with ether in a Stokes's tube, after treatment with 30 per cent hydrochloric acid in a boiling water-bath for 10 minutes. The ether extract was dried and weighed, to give the fat content of one gram of dried stool, this was multiplied by the total calculated weight of dry stool, to give the total fat excretion for the period.

Results

General considerations affecting interpretation. As work on the lines outlined above proceeded, it became clear that the results did not lend themselves to simple interpretation. The two main causes of difficulty were the unexpected variability in fat output from period to period and the occasional occurrence of unpredictable spontaneous improvement.

Variability of fat output. Although duplicate estimations showed that the error of estimation of the fat in the dried stool was less than five per cent, it was found that successive four-day periods might differ in their apparent fat output by as much as 50 per cent. Figures illustrating this variability cannot be given here, but are presented in a report to GHQ (India), to be published later. The variability was considerably lessened when carmine and iron markers were used, but the chief method of overcoming the variability of fat output over short periods was to use periods of adequate length, that

is, to group three periods of four days into a single 12-day period for interpretation Bassett, Keutmann, Hyde, Van Alstine, and Russ (1939), also found it necessary to use long periods The conclusions reported here are all based on 12-day periods, except in a few cases specified in the tables where treatment had to be begun early or the patient left hospital

Spontaneous improvement This is not uncommon in patients with sprue who are at rest in bed on a controlled diet It is therefore always possible that an observed improvement may coincide with, rather than result from, a given treatment This consideration does not interfere with the interpretation of negative results of treatment In the case of yeast extract, in which the early results suggested a positive action on fat absorption, we used in the later cases a double preliminary period, so that any spontaneous improvement which was going to occur might become apparent Five cases did appear to be improving during this long preliminary period, and these were kept under observation in order to assess the degree of improvement likely to occur spontaneously under the conditions of our experiment It is to be noted that these cases form a selected group, and if anything give an exaggerated impression of the extent to which improvement can occur without specific treatment

Minor difficulties in interpretation arise from the occasional incidence of watery diarrhoea, from the change in some patients from a 65-gm fat diet to a 96-gm diet, and from the possibility that part of the faecal fat is a true excretion and not unabsorbed food-fat Patients with watery diarrhoea were excluded from the series until the diarrhoea had been controlled by liver treatment or sulphaguanidine, watery stools with solid particles cannot be fairly sampled, and diarrhoea itself affects fat absorption With regard to dietary variation, it was found in five patients that change of diet from 69 gm to 96 gm of fat per diem did not affect the percentage fat absorption enough to interfere with interpretation of fat balance results (Black, Fourman, and Trinder, 1946) It was also found that on a fat-free diet sprue patients excreted no more fat than normal subjects, so excreted fat as opposed to unabsorbed fat represents only a small systematic error which does not affect significantly the comparison of successive periods

Fat Absorption in Untreated Sprue

In 19 patients who were observed for an adequate period before starting treatment, the percentage fat absorption varied from 51 to 85, with a mean of 75.6, and a median of 80 In normal persons fat absorption exceeds 90 per cent of the intake It is probable that most of the faecal fat in such persons is excreted fat, and not unabsorbed food fat (Hill and Bloor, 1922) Excreted fat forms a smaller proportion of the faecal fat in the sprue stool, in which unabsorbed food fat is much higher than in normal persons It is of some interest that severe steatorrhoea can occur when by far the greater part of the fat in the diet is being absorbed, a 10 per cent failure in fat absorption

is enough to double the normal daily output of fat in the stools. From the point of view of assessing treatment, the wide variation between fat absorption in different patients is of less importance than the changes which a single patient is likely to show from one period to the next without change in treatment. Our data on this question are necessarily limited, for fairly long periods are required, and many patients cannot be left for 24 days without

TABLE I

Percentage Fat Absorption in Consecutive Periods without Treatment

Case	Period 1		Period 2		Difference in percentage fat absorption between the periods
	Duration (days)	Percentage fat absorption	Duration (days)	Percentage fat absorption	
8	12	80.0	7	81.6	+1.6
9	8	85.2	8	84.4	+10.2
12	12	85.7	12	82.7	-3.0
22	12	80.0	12	85.2	+5.2
26	8	82.8	12	85.5	+2.7

specific treatment. The five patients represented in Table I are therefore a selected group, in that they were either improving clinically, or at least not deteriorating. It will be seen that the only definite difference in fat absorption from one 12-day period to the next was an increase of 19 per cent in Case 9. Analysis of the difference of 5.2 per cent in Case 22 shows that it is not significant, in view of the variability of the data on which it is based. It follows from this that observations on single cases by this method are of no value, unless the differences are gross, our subsequent conclusions are therefore based on series of comparably treated cases.

Nicotinic Acid and Riboflavine

Table II gives the fat absorption figures in two patients treated with nicotinic acid, 50 mg thrice daily, and in four patients treated with nicotinic acid, 50 mg thrice daily, and riboflavine, 5 mg daily, these drugs were given intramuscularly. In none of the six patients was there any significant individual change in fat absorption, but taking the series as a whole, there was a small drop in fat absorption in five of the six instances. The figures for the four patients who had both nicotinic acid and riboflavine were analysed together, and the probability of the fall being due to chance is 0.1. There was therefore no evidence that nicotinic acid and riboflavine improved fat absorption, and some evidence that fat absorption may actually have been depressed. Since the two cases treated with nicotinic acid alone also showed a deterioration of the same order, it seems likely that in the combination of the two drugs it was the nicotinic acid which was responsible. No clinical improvement was observed with nicotinic acid or riboflavine. These results conflict with the claims of Manson-Bahr (1940). As Stannus (1942) pointed out, most of Manson-Bahr's cases were having liver treatment at the same

time as nicotinic acid, and this could account for the improvement which he observed. Tongue and mouth signs which are often attributed to deficiencies of nicotinic acid and riboflavin are undoubtedly found in some cases of sprue, these signs are less prominent in early cases, such as we were mainly studying, and it is possible that favourable local results might be caused by nicotinic acid or riboflavin therapy in cases with well-established secondary

TABLE II

Effect of Nicotinic Acid and Riboflavin on Fat Absorption

Case	Period 1		Period 2		Difference in percentage fat absorption between the periods
	Duration (days)	Percentage fat absorption	Duration (days)	Percentage fat absorption	
6	12	79.5	9	74.8	-4.7
9	12	79.8	8	70.4	-9.4
12	12	89.4	12	79.8	-9.6
14	12	77.2	12	75.2	-2.2
15	12	80.0	12	73.6	-6.4
17	12	79.2	12	82.3	+3.1

Note—Period 1 in all cases was without treatment. In Period 2 all patients were given 50 mg of nicotinic acid thrice daily, in addition, cases 12, 14, 15, and 17 were given 5 mg of riboflavin daily.

deficiencies of these vitamins. Our own results suggest that the fundamental anomaly in sprue, the failure of fat absorption, is not influenced by such therapy. Intensive therapy with single vitamins may even be harmful, by accentuating a multiple vitamin deficiency, so-called 'vitamin imbalance' (Morgan, 1941).

Liver Extract

The value of liver extract in the treatment of sprue is well established. Castle, Rhoads, Lawson, and Payne (1935) showed that the anaemia of sprue responded to liver extract, some cases responded to liver by mouth, in others the liver had to be given parenterally. Rodriguez-Molina (1943) found that the tongue signs, anaemia, and gastro-intestinal disturbance of sprue all responded to parenteral liver extract, he used a daily dose of five to 10 c.c. of an extract, each c.c. of which was equivalent to only five gm. of fresh liver. The size of the dose and the crudeness of the extract used are worth noting, for failure in the liver treatment of sprue has been known to occur through inadequate dosage or the use of the refined liver extracts which are appropriate to the treatment of pernicious anaemia. Barker and Rhoads (1937) found that large doses of crude liver extract given by injection improved the absorption of fat in sprue, as judged by the serum-lipide curve after a fatty meal. Serum-lipide curves are open to some criticism in that the normal range is wide, and that they can measure only the rate of fat absorption and not the total amount (Black and Simpson, 1947). We have observed by the balance technique the effect of liver extracts on fat absorption in eight patients, four of whom were used for more than one trial, so that Table III

gives the results of 12 such experiments, each based on two successive 12-day periods. Three liver extracts were used —

(1) 'T C F' An Indian preparation, the only one available to us for some months, described as containing 'most of the B-complex substances present in the original liver', and as 'a pre-Cohn fraction G'. We were unable to discover how much liver each c.c. of this extract represented, but it was

TABLE III

Effect of Liver Extract on Fat Absorption in Successive 12-day Periods

Case	Treatment	Period 1		Period 2		Difference in percentage fat absorption between the periods
		Percentage fat absorption	Percentage fat absorption	Treatment	Percentage fat absorption	
2	None	50.7		T C F	47.0	-3.7
24	"	79.5		"	81.0	+1.5
23	"	38.5		Hepastab	82.0	-6.2
12	Nicotinic acid, riboflavine	70.8		Nicotinic acid, riboflavine, T C F	83.7	+3.9
15	" "	73.6		" "	78.0	+4.4
17	" "	82.8		" "	83.4	+0.6
14	T C F	57.2		Hepatex-T, T C F	60.4	+3.2
15	"	78.0		" "	79.6	+1.6
17	"	83.4		" "	82.9	-0.5
20	"	69.9		" "	82.1	+12.2
12	"	82.8		Hepastab, T C F	87.5	+4.7
24	"	81.0		" "	81.8	+0.8

Note—The dosage of liver is given in the text, Case 2 had 2 c.c. of T C F daily instead of the usual 4 c.c.

found to be effective in the clinical treatment of sprue, suggesting that it was fairly crude, though it was certainly not so crude as the preparation described by Rodriguez-Molina (1943).

(2) 'Hepastab' (Boots) A moderately refined liver extract

(3) 'Hepatex-T' (Evans) An extract containing the whole of the vitamin B complex naturally present in liver, and also added thiamine and nicotinic acid. This preparation is designed for the treatment of tropical macrocytic anaemia.

The standard dosage used was 4 c.c. daily for all preparations, and in all cases a loading dose of 40 c.c. spread over four days was given at the beginning of liver treatment, all doses were given intramuscularly. When Hepastab and Hepatex-T became available, they were used in order to see whether they would produce an improvement in fat absorption which we had failed to find with the less well-defined Indian preparation. With the exception of one trial of Hepatex-T (Case 20), there was no significant improvement in fat absorption, and the improvement of 12.2 per cent in one case out of eight, although statistically significant, could easily have been spontaneous (see Table I). Bassett, Keutmann, Hyde, Van Alstine, and

Russ (1939) also failed to demonstrate any improvement in fat absorption with liver treatment of idiopathic steatorrhoea. These negative results stand in contrast to the striking clinical improvement shown by the patients on liver treatment. They gained weight rapidly, their appetite improved, tongue signs disappeared, and they felt very much better. Liver extract also improved diarrhoea in those patients who had it, for reasons already given,

TABLE IV

Effect of Continued Liver Treatment (5 to 7 weeks) on Fat Absorption

Case	Period 1 (before treatment) Percentage fat absorption	Period 2 (after 5 to 7 weeks of liver) Percentage fat absorption
4	75	79
11	61	77
14	75	81
15	80	79
17	79	83
19	77	84
20	70	82
24	80	87
Mean	74.8	81.5
Standard deviation	± 6.44	± 3.21
Difference between means 6.9		
Standard error of difference ± 2.54		
The difference between the means is statistically significant		

such patients have not been included in the fat-absorption series. Moreover, we found that patients who were kept on liver treatment for a month or more showed a gradual improvement in fat absorption (Table IV). The striking feature is that with doses of liver extract sufficient to produce rapid clinical improvement, there is so small and gradual an effect on the fat absorption defect. This finding will be discussed later in relation to our results with yeast extract.

Yeast Extract

The preparation used was 'Vegemite', which resembles 'Marmite' and is manufactured in Australia. It was given in a dose of 5 gm four times a day. The effect of treatment with yeast extract on fat absorption is shown in Table V. In all cases, the patients who were given yeast extract were also on either 4 c.c. or 2 c.c. of liver extract daily, the reasons for this procedure were as follows:

(1) It has already been shown that liver extract in the dosage used, given over a period of less than a month, does not improve fat absorption demonstrably, so that any observed improvement within this period can be ascribed to the added yeast extract.

(2) As far as possible, severely ill patients were chosen for this study, to lessen the chances of spontaneous improvement. Such patients are liable to diarrhoea, with rapid deterioration in their general condition, and such relapses can be controlled or prevented by liver treatment.

gives the results of 12 such experiments, each based on two successive 12 day periods. Three liver extracts were used —

(1) 'TCF' An Indian preparation, the only one available to us for some months, described as containing 'most of the B-complex substances present in the original liver', and as 'a pre-Cohn fraction G'. We were unable to discover how much liver each c.c. of this extract represented, but it was

TABLE III

Effect of Liver Extract on Fat Absorption in Successive 12-day Periods

Case	Treatment	Period 1	Treatment	Period 2	Difference in percentage fat absorption between the periods
		Percentage fat absorption		Percentage fat absorption	
2	None	50.7	TCF	47.0	-3.7
24	"	79.5	"	81.0	+1.5
23	"	38.5	Hepastab	82.0	-6.2
12	Nicotinic acid, riboflavine	79.8	Nicotinic acid, riboflavine, TCF	83.7	+3.9
15	" "	73.6	" "	78.0	+4.4
17	" "	82.8	" "	83.4	+0.6
14	TCF	57.2	Hepatex-T, TCF	60.4	+3.2
15	"	78.0	" "	79.6	+1.6
17	"	83.4	" "	82.9	-0.5
20	"	69.9	" "	82.1	+12.2
12	"	82.8	Hepastab, TCF	87.5	+4.7
24	"	81.0	" "	81.8	+0.8

Note — The dosage of liver is given in the text, Case 2 had 2 c.c. of TCF daily instead of the usual 4 c.c.

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The standard dosage used was 4 c.c. daily for all preparations, and in all cases a loading dose of 40 c.c. spread over four days was given at the beginning of liver treatment, all doses were given intramuscularly. When Hepastab and Hepatex-T became available, they were used in order to see whether they would produce an improvement in fat absorption which we had failed to find with the less well-defined Indian preparation. With the exception of one trial of Hepatex-T (Case 20), there was no significant improvement in fat absorption, and the improvement of 12.2 per cent in one case out of eight, although statistically significant, could easily have been spontaneous (see Table I). Bassett, Keutmann, Hyde, Van Alstine, and

(3) Since no yeast extract suitable for parenteral injection was available to us, liver extract was given to ensure that any favourable action of yeast extract should not be prevented by a secondary absorption defect, such as may occur in sprue and be amenable to liver therapy

Of the 12 patients represented in Table V the first six were put on yeast extract after 32 days or less on liver treatment, and their fat absorption in the first preliminary observation period ranged from 62 to 80 per cent. The other six patients had all had liver for a longer period before yeast extract was started, and their initial level of fat absorption also tended to be higher, and in two cases was over 80 per cent. The patients in the second group showed a less definite response to yeast extract, except for Case 27 whose fat absorption had remained at low level in spite of fairly prolonged liver treatment. This is partly because long-continued liver treatment may supply an adequate dose of factors similar to those in yeast extract and partly because it is easier to demonstrate improvement in a patient with poor fat absorption than in one who is nearly normal, as the absolute amount of fat involved is larger. Dr C C Spicer has made a statistical analysis of the fat-excretion figures for the first six patients in Table V, that is, those patients who had been receiving liver for not more than 32 days before yeast was added to their treatment. There was a significant fall in the fat excretion in the yeast extract period, the data did not show any progressive trend in the preceding (control) period, such as might be expected if the improvement in Period 3 were the result of a gradual change occurring independently of the new treatment. In individual patients, the variance in the fat excretion per three- or four-day period was significantly smaller when the patients were having yeast extract.

Discussion

The estimation of percentage fat absorption over 12-day periods is a useful method of assessing the severity and following the progress of steatorrhoea. None of our patients with untreated sprue had a fat absorption higher than 85 per cent, which is well below the normal value of 90 per cent or more, in contrast, we found considerable overlap in blood-fat curves between sprue patients and normal controls (Black and Simpson, 1947), and many patients with early sprue had a normal chylomicron count (Fourman, 1947). We believe that to assess the effect of treatment on fat absorption some adequate form of fat-balance must be carried out in spite of its tedium, and the variance of three- or four-day periods is such that long observation periods are required. Expressing the results of a fat-balance as 'percentage fat-absorption' shows clearly that the fat-absorption defect in sprue is only partial, in the most severe impairment observed, just over half the ingested fat was still being absorbed. It should be remembered, however, that a percentage fat absorption of 80 per cent, which appears a very mild defect, still implies that more than twice the normal amount of fat is being excreted in the stools, while a fat absorption of 60 per cent implies four times the normal amount of fat in

TABLE V
Effect of Yeast Extract on Fat Absorption

Case	Duration of liver treatment before yeast extract (days)	First preliminary period			Second preliminary period			Yeast extract period			Difference in percentage fat absorption		
		Dura- tion (days)	Treat- ment	Percentage fat absorption	Dura- tion (days)	Treat- ment	Percentage fat absorption	Treatment	Percentage fat absorption	Period 2 minus Period 1	Period 2 minus Period 3	Period 1 minus Period 2	Period 1 minus Period 3
3	0	6	None	73.0	12	Nicotinic acid	68.8	Nicotinic acid, liver, yeast extract	83.1	-4.2	+14.3		
6	0	12	"	70.5	12	"	83.5	"	90.5	+4.0	+7.0		+7.0
8	0	9	"	80.2	11	None	80.8	"	85.5	+0.6	+4.7		+4.7
25	14	8	Liver	72.7	8	Liver	68.6	Liver, yeast ex- tract	72.8	-4.1	+4.2		+4.2
28	28	12	"	65.8	12	"	69.0	"	80.4	+3.2	+11.4		+11.4
2	32	12	"	62.0	12	"	64.6	"	71.6	+2.6	+7.0		+7.0
4	37	12	"	73.8	12	"	70.4	"	82.3	+5.0	+2.9		+2.9
24	43	12	"	83.5	12	"	86.0	"	87.2	+3.1	+0.6		+0.6
27	45	12	"	64.8	12	"	63.2	"	68.7	-1.6	+5.5		+5.5
17	47	8	"	80.4	8	"	87.2	"	86.1	-2.2	-1.1		-1.1
15	49	8	"	76.4	8	"	80.7	"	81.1	+1.3	+0.4		+0.4
14	63	8	"	74.7	8	"	83.6	"	84.1	+8.9	+0.5		+0.5

Note—All the yeast extract periods were of 12 days

5 When yeast extract was given by mouth in large doses some improvement in fat absorption occurred within 12 days Yeast extract may be of value in the maintenance treatment of returned patients with tropical sprue

We are indebted to Mr C K Dilwali and Dr C C Spicer for valuable help in the statistical treatment of our data

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the stools. The absorption defect in our cases of early tropical sprue is of the same order as that detected by similar methods in idiopathic steatorrhoea (Bassett, Keutmann, Hyde, Van Alstine, and Russ, 1939, Cooke, Elkes, Frazer, Parkes, Peeney, Sammons, and Thomas, 1946)

The use of nicotinic acid and riboflavine without liver injection had no favourable effect either on the patients' clinical condition or on their fat absorption. Liver injection in adequate doses was followed by rapid clinical improvement, in contrast to this, fat absorption under liver treatment was not appreciably affected for some weeks, although with long-continued liver treatment there may be gradual improvement in fat absorption. When yeast extract was given in large doses by mouth to patients on liver treatment there was a much more rapid improvement in fat absorption. In explaining this phenomenon we incline to the view that it is a dose-effect, the much larger amount of yeast which can be given by mouth, as compared with liver by injection, is likely to contain more of whatever substance is active in improving fat absorption in sprue. Liver almost certainly contains some of this substance, since long-continued treatment with large doses of liver is attended by improved fat absorption. Folic acid improves the anaemia of sprue, and also the diarrhoea (Spies, 1946). Davidson, Girdwood, and Innes (1947) reported improvement in fat absorption in one of two cases of tropical sprue studied with a three-day balance technique. Much more extensive observations are required on this question, but it is possible that the improvement in fat absorption in our cases with yeast extract may have been partly due to its folic acid content. From a practical point of view yeast extract by mouth deserves a place in the maintenance treatment of patients who have had sprue in the tropics and have returned to this country but continue to have steatorrhoea. Our experimental data suggest that it is more effective in improving fat absorption than any dose of liver which can conveniently be given over a long period.

Summary

1 Fat-balance experiments were carried out on 28 patients with early tropical sprue. The results were expressed as 'percentage fat absorption' $\left(\frac{(\text{dietary fat} - \text{faecal fat})}{\text{dietary fat}} \times 100 \right)$. The interpretation of such results is discussed in relation to the day-to-day variation in fat output and the possibility of spontaneous improvement, the use of 12-day periods is recommended.

2 In untreated sprue fat absorption ranged from 51 to 85 per cent, normal fat absorption is over 90 per cent.

3 Nicotinic acid and riboflavine given by injection did not cause clinical improvement nor increase fat absorption.

4 Adequate parenteral liver treatment was followed by gain in weight and clinical improvement, but improvement in fat absorption was not appreciable for some weeks.

5 When yeast extract was given by mouth in large doses some improvement in fat absorption occurred within 12 days Yeast extract may be of value in the maintenance treatment of returned patients with tropical sprue

We are indebted to Mr C K Dilwali and Dr C C Spicer for valuable help in the statistical treatment of our data

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HEREDITY IN HYPERTENSION¹

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It is not a new observation that a family history suggestive of high blood-pressure is commonly elicited from patients with essential hypertension, for Morgagni in 1769 mentioned the case of Zani who died of cerebral haemorrhage and whose father 'had died of an apoplexy'. Close inquiry will often reveal that in the family hypertensive disease has affected one or both parents and one or more of the siblings. The histories of Cases 5, 14, 16, and 33 in the Appendix to the present paper are characteristic and striking examples. If this family predisposition to hypertension be acknowledged, it is at first sight strange that the hereditary factor has not been fully worked out and generally recognized, for the immediate assumption is that we may be dealing with a simple Mendelian transmission of dominant type. There are, however, many reasons why the study of the heredity of hypertension presents difficulties. One is the intrinsic difficulty in all problems of human genetics, namely, that of simultaneously studying several generations. In hypertension, which is often not manifest until middle age, this difficulty is magnified, for almost without exception the affected parent is dead before the patient comes under observation, and the patient's offspring are too young to have developed the disease. Added to that is the fact that the testing of blood-pressure in general practice has become a routine only during the last 15 or 20 years. We have thus only too often to be content with the patient's statement that the parent died of heart failure, dropsy (presumably cardiac), seizure, stroke, apoplexy, or Bright's disease. Since the majority of cases of hypertension succumb to heart failure rather than to cerebral haemorrhage or uraemia, a history of death from cardiac disease must be considered important. Such evidence could not be deemed acceptable if it occurred only in a moderate number of histories, especially having regard to the frequency of hypertension in later life, but if we are dealing with a dominant Mendelian character the history should be obtainable for one or both parents of practically every case, and if this were so it would indeed be convincing. Exceptions would occur where one parent had died of other causes at an early age, before hypertension could be expected to develop, and there might be very occasional anomalies due to illegitimacy. There is the further possibility, or even likelihood, that the gene conveying hypertension has a 'rate of expression' of less than 100 per cent, and is dependent upon other genetic or environmental factors for its effects to become manifest. There is another and much more cogent reason why a history of hypertensive disease in a parent might not be found, and that is that hypertension is not an

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entity but a syndrome with many causes. The differentiation of essential hypertension from renal hypertension (chronic nephritis) has been made for many years, but it is only comparatively recently that the importance of what might be called the obscure renal causes of hypertension has been realized. Of these, chronic pyelonephritis, often in a healed stage without active infection, is probably the most important, and Weiss and Parker (1939) in their well-known monograph claim that it is the basis of at least 15 to 20 per cent of cases of so-called malignant hypertension. Wosika and Maher (1939) reviewed 600 cases of hypertension urologically and decided that 71 per cent were 'essential' and 29 per cent secondary to demonstrable renal causes. Schroeder and Steele (1939) in a similar survey of 218 cases put 26 per cent into the renal group, and Harrison and Williams (1939) found some disorder of the urinary tract in 30 of 100 cases of supposed essential hypertension. Weitz (1923), who studied the heredity of hypertension in 82 personal cases, found a suggestive family history in 76 per cent. Hines (1937) found it in 86.6 per cent. If these observations are put together the attractive possibility is immediately suggested that the cases without family history are not essential hypertension. It is with a view to testing this hypothesis that the present study has been made.

After this preamble we may turn to a brief consideration of the evidence required to prove that essential hypertension is the heterozygous (or occasionally homozygous) expression of a dominant Mendelian characteristic, and the observations which have been made on the subject up to the present time.

1 *Where one parent is affected, half the children should also develop the disease, and more than half if both parents are affected.* This is extremely difficult to prove in human hypertension because of the age of onset. If the patient, perhaps aged 58 years, is the oldest of six siblings, the youngest may be only 42 and may not yet show hypertension. This, with the difficulty of assembling the siblings in sufficient numbers and taking their blood-pressure (for without an actual reading the evidence is valueless), renders such a study almost impossible. A further difficulty in testing subjects not complaining of hypertensive symptoms is to decide what constitutes hypertension. Weitz (1923), nevertheless, attempted a study of actual blood-pressure readings in all the available elder siblings of his hypertensive patients. Of 47 elder brothers and sisters of 30 patients, 27 had a systolic pressure under 150, 29 up to 160, and 18 over 160. Eleven elder brothers and sisters had, however, already died of heart failure or apoplexy. On the other hand, had they lived, some might not have been available for testing. Some who died of other causes might also not have been available. Assuming that on the whole these cases would have increased the number of hypertensives, the figure of 27/30 (taking 150 systolic as the border-line of hypertension) or 29/38 (taking 160 as the limit of normality) would approach nearer to a ratio of 1/1. Ayman's (1933) study of three generations of a hypertensive family shows proportions similar to those which would be expected of a Mendelian dominant character, but is open to the difficulty of deciding what

is to be considered as hypertension, especially in the younger members of the family. Only one member of the three generations had a diastolic pressure of more than 100.

2 *All affected persons should have at least one affected parent.* Weitz (1923), whose data on this subject are the most complete, found that one or both parents died of heart disease, angina, dropsy, or stroke in 63 of 82 cases (76.8 per cent). Of the remaining 19 only four (4.9 per cent) had both parents living to 60 years and over, whereas in 267 controls without symptoms of hypertension, 33.7 per cent had both parents living to be 60 without cardiac or cerebral symptoms. A positive family history of cardiovascular disease was obtained in only 30.3 per cent of the controls. Hines (1937) made an exhaustive study of the relatives of hypertensive and non-hypertensive patients, using the cold pressor test to determine a hypertensive tendency in the younger members of the families. He found a family history of cardiovascular disease in 86.6 per cent of the hypertensives, in 84.2 per cent of the hyperreactors to the cold pressor test, and in only 17.2 per cent of the hyporeactors.

3 *All the children of unaffected parents should be normal.* In the case of human hypertension the data so far collected allow of proof only in a negative sense, namely, by demonstrating the essential truth of proposition 2 above.

4 *Direct transmission through three generations (in the absence of marriage of blood-relations) is practically proof of dominant heredity.* (Roberts, 1940) This has been shown in the family recorded by Ayman (1933) and in several of the families in the paper by Weitz (1923).

5 If the rate of expression is less than 100 per cent the incidence in parents and siblings should be the same. This is almost exactly realized in Weitz's data.

It seemed to the author that considering the difficulties of study in a condition of this kind, the best contribution that could be made to the subject at this stage would be an analysis of 100 or more cases of hypertension with a view to determining whether the ones without a family history were those in whom hypertension was not of primary or essential type. Since we have to rely on patients' statements rather than on measurable data, it is important that the relevant details of each case should be given, hence the somewhat bulky appendix to the present paper. The patients were unselected except in two respects. Clear cases of nephritic hypertension were excluded, and, in view of the doubt as to what constitutes a normal blood-pressure, it was decided from the beginning that the evidence of hypertension should be unequivocal. The actual figures are given in each case. So as not to set an arbitrary standard, only patients with symptoms referable to hypertension were included. In every case the diastolic blood-pressure was 100 or over. Nevertheless, the series in no sense represents a random sample of the hypertensive community, for in a large teaching hospital elderly persons suffering from the minor effects of a benign hypertension long sustained are rare. The series no doubt includes a far bigger

proportion of the hypertensive rarities and extremes than would be found, for example, in a survey taken from general practice

Actually 116 cases have been studied, and are divided into four groups. Group 1 comprises those in whom the evidence of hypertension in one or both parents is very strong or, if the evidence is uncertain, is supported by a history of hypertensive disease in siblings of parents or patients. Group 2 comprises those in which the evidence points only to a reasonable probability of hypertensive disease in one or both parents. This includes most of those in which the parent died early or suddenly of heart failure. Group 3 comprises those cases in which the evidence is lacking, for instance nothing is known of the cause of death of a parent, or the death occurred from some cause other than hypertension at an early age (that is, younger than the present age of the patient). These cases neither support nor refute the hypothesis. Group 4 comprises those in which the evidence is against hypertensive disease in either parent. All the data concerning the family history were collected personally by the author. This is of great importance, as is well shown by Case 19, in which the House Physician's notes stated that the father had died of bronchitis. On inquiry the patient stated that her father's illness started with nose-bleeding, followed by rapid deterioration of vision which could not be corrected by glasses. This was followed by shortness of breath and death from 'bronchitis'. The illness lasted several months. In addition to the study of 116 cases of hypertension, family histories were taken from 71 unselected patients without hypertension. Only patients over the age of 30 years were used for this purpose. They are referred to in the Tables as the Control Group.

Analysis of the final diagnosis in the 116 cases of hypertension is not easy, because some of those who appeared to have essential hypertension also gave a history of pyelonephritis or other renal disorder in the past. Evidence will be presented later that in such cases a strong family history of hypertension argues in favour of the case being one of essential rather than secondary hypertension, but it is not admissible to use such evidence as a proof of its validity. The cases are therefore primarily divided into those in which essential hypertension appeared to be the only tenable diagnosis (78 cases), and the remainder in which secondary hypertension was either definite (for example, polycystic kidney and periarteritis nodosa) or at least possible.

The distribution is as follows

Essential hypertension (benign 61, malignant 17)	78
Probably essential hypertension (benign)	4
Secondary hypertension	
Pyelonephritis 9}	18
Other causes 9}	
Uncertain whether essential or secondary (pyelonephritis 8, calculus 2)	10
Diagnosis doubtful (Cases 59, 68, 107, 111, 112, 113)	6
	<hr/> 116

Table I shows the analysis of these cases and of the Controls grouped according to their family histories, and Figs 1 to 4 show that the distribution in essential hypertension is totally different from the distribution in secondary hypertension, which closely simulates that of the Control Series. Age is of course a factor in family history. Young persons are much more likely than old ones to have two living parents. The average ages are, therefore,

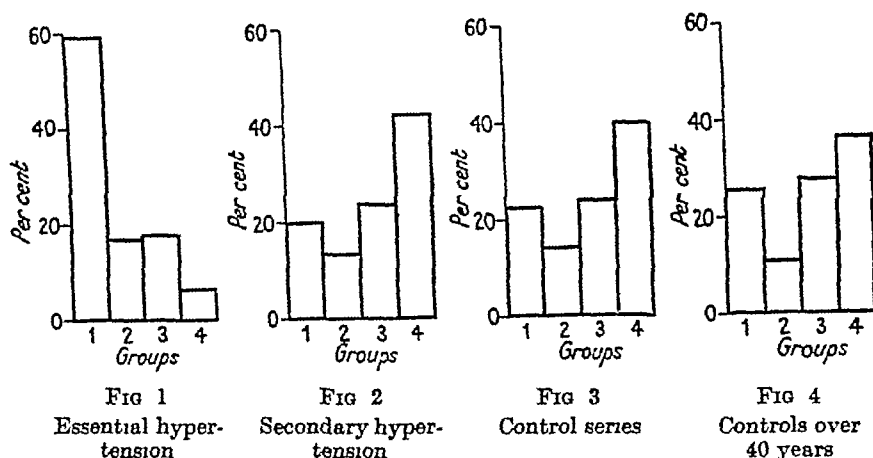


TABLE I

Family history	Hypertension (all cases)		Essential hypertension only		Other hypertensives only		Control series		Controls over 40 years	
	No	%	No	%	No	%	No	%	No	%
Group 1 (Positive)	54	46.6	46	59.0*	8	21.1	16	22.5*	14	25.5
Group 2 (Probable)	18	15.6	13	16.7	5	13.2	10	14.1	6	10.9
Group 3 (Incomplete)	23	19.8	14	17.9	9	23.7	17	23.9	15	27.3
Group 4 (Negative)	21	18.1	5	6.4†	16	42.1	28	39.4†	20	34.6
Totals	116		78		38		71		55	

* Standard error of difference = 7.5 † Standard error of difference = 6.4

Differences in Groups 2 and 3 throughout are not significant

(See also Addendum on p. 121)

given in Table II, and will be seen to be comparable. In the second Control Group cases under the age of 40 years have been omitted to bring the average age into line with that of benign hypertension. Summarizing from the point of view of heredity it will be seen that about 76 per cent of cases of essential hypertension gave a family history suggestive of hypertension, and in only 6.4 per cent (five cases out of 78) did the family history appear to speak against hypertension. In the remainder the data are not obtainable. In the secondary hypertension group and the Control Group these figures are approximately 35 and 39 per cent respectively. These results closely

correspond with those of Weitz (1923) If essential hypertension were inherited by a simple Mendelian dominant transmission there should be no cases with a negative family history (Group IV) The exceptions must therefore be further scrutinized

Case 97 is a young woman of 35 years, the youngest case in this series to be classified as benign hypertension She has severe hypertension with no papilloedema A sympathectomy has given opportunity for biopsy study of both kidneys Histologically they are peculiar in showing only the slightest

TABLE II

Ago distribution	Average ago	Range	Number of cases
Malignant hypertension	47	34 to 58	17
Benign hypertension	55	35 " 76	61
Other hypertensives	44	26 " 66	38
Control series	49	30 " 73	71
Controls over 40 years	53	40 " 73	55

evidence of pathological change at all, occasional glomerular sclerosis There is no histological evidence on which the pathologist could base a diagnosis of hypertension, either benign or malignant In this the sections differ from any other biopsy material we have seen, and it is possible that there is some endocrine factor at work, although so far there is no clinical evidence to support such a view, except that the patient developed mild symptoms of hyperthyroidism temporarily during thiocyanate treatment It has not been possible to investigate the parents

Case 99 appears to conform to the characteristics of malignant hypertension This was a man of 50 years whose father died of pneumonia at 64 The possibility of hypertension in the father cannot be ruled out

Case 105, another man of 50 years with malignant hypertension, has been most carefully searched for evidence of renal pathology without success Biopsy during sympathectomy (on one side only at the time of writing) shows changes indicating early malignant hypertension This appears to be the one absolute contradiction to the hereditary rule postulated

Case 108 is a young woman of 36 years with extreme obesity (18 stone) which may be an important factor in her hypertension

Case 110 is a young man of 35 years in whom the hypertension was discovered accidentally and the symptoms were probably psychogenic Rest and reassurance in hospital restored the blood-pressure to normal His father died of cancer at 56 years and it seems not unlikely that the patient may live at least as long

Group IV also contains three cases in which the diagnosis appears doubtful In Case 112 there is strong evidence of renal pathology but the patient refused further investigation

Case 111 was complicated by bronchial carcinoma The patient was unintelligent and unco-operative and the data are incomplete

Case 113 is peculiar At the age of 18 years he had pneumonia and empyema He is known to have had hypertension from the age of 23 to

27 years He then had a hemiplegia and was admitted to hospital While in hospital he had an attack of severe abdominal pain associated with transient jaundice and signs of intestinal ileus The blood-pressure fell to 140/90, but after some days he slowly regained strength and his blood-pressure returned to 210/140 Periarteritis nodosa is considered to be a possibility

Discussion of Heredity

It is impossible from the data which can be assembled in this way to produce anything like proof that essential hypertension is conveyed as a Mendelian dominant The most that can be said is that the facts are compatible with such a hypothesis, that the great majority of cases in which the rule does not seem to hold are not essential hypertension at all, and that careful investigation will reveal a hereditary factor in over 90 per cent of cases of essential hypertension in which the necessary data are obtainable Unfortunately in about 20 to 25 per cent of all hospital patients either the mode of death of a parent is unknown, or death at an early age from some other cause makes evidence for or against a hypertensive heredity unobtainable Nevertheless the realization of the importance of heredity in essential hypertension has a very practical outcome On the data assembled here it is possible to say that in a case of hypertension of uncertain origin a strongly suggestive family history (Group 1) provides nearly a 6 to 1 chance that the case is one of essential hypertension, whereas if the history gives strong evidence against hypertension in the parents (Group 4) the chances are more than 3 to 1 in favour of some other cause of hypertension being found, and the case should be thoroughly investigated in order to establish an accurate diagnosis This is particularly important in the search for cases of hypertension with unilateral renal pathology in which a cure by nephrectomy may be possible It is interesting that in compiling a review of the literature of unilateral renal disease and hypertension (Langley and Platt, 1947), 23 cases were found in which the family history was reported Of these 11 gave a positive family history of hypertension and 12 a negative history Of the 11 with a positive family history only one was cured by nephrectomy Of the remaining 12 no less than eight were successful

The realization of the great importance of heredity moreover makes one cautious in accepting the loose statements which tend to be made from time to time on the importance of environmental factors, especially psychological trauma, on the development of hypertension There are those who seek to place essential hypertension amongst that popular group, the psychosomatic disorders If so, then the psyche is evidently as heritable as the soma We have seen no evidence in studying the present series of cases that psychological factors have played any part in the causation of the disorder, except that in certain cases a mild anxiety state is liable to be induced by the patient's realization that he has a high blood-pressure Further study on this subject is being undertaken

Before leaving the subject of heredity, the question of whether the homozygous form of hypertension can be distinguished from the heterozygous should be considered. In cases in which hypertension probably existed in both parents we have been unable to discern any tendency for hypertension to occur in a particularly severe form in any of the offspring, and Case 5 demonstrates that severe malignant hypertension can occur at an early age in a patient who is certainly heterozygous, as her father's blood-pressure is known to have been low. Malignant hypertension is not therefore the homozygous expression of the gene. We have not personally found a family in which all the siblings were known to have hypertension, neither is any such family recorded by Weitz (1923).

Finally, we are not prepared to say whether the inherited factor is specific for hypertension or is merely a tendency to arterial or arteriolar change affecting in some instances the renal vessels and in others the coronary or cerebral circulation. In 12 of our 59 instances of essential hypertension with positive heredity the only evidence was that of cardiac disease in the family. Since hypertension is the common accompaniment of heart failure and of coronary disease (69 per cent. according to Cassidy (1946)) in the middle-aged or elderly, there is a probability, but by no means a certainty, of hypertension in these cases. The final word on this subject must await long-term studies of hypertension with actual blood-pressure determinations in several generations.

Classification of Hypertension

The study of this group of 116 hypertensives has provided some data on matters other than heredity, which may be briefly presented. Of the causes or possible causes of secondary hypertension, when chronic nephritis is excluded, pyelonephritis appeared to be by far the most frequent, and occurred in 17 case histories. Other causes were uncommon—renal calculus 3 instances, polycystic kidney 2, other congenital abnormalities 2, periarteritis nodosa 2, pregnancy toxæmia 2, Morgagni-Morel syndrome 1 (Case 114). This list does not of course exhaust the interesting possibilities in the pathogenesis of hypertension.

It is often difficult to make a clinical diagnosis between chronic (healed, atrophic) pyelonephritis and essential hypertension. It appears from the few instances encountered in the present series that when renal insufficiency with hypertension is not accompanied by papilloedema, secondary hypertension may be suspected (Cases 50, 54, and 70), but there are of course cases of chronic pyelonephritis in which renal function is maintained (for example, Case 91) and others in which both papilloedema and renal failure occur (Cases 98 and 100). Case 2 is exceptional in being apparently a case of essential hypertension with renal failure but without papilloedema. Even at autopsy the characteristic arteriolar changes of malignant hypertension were not demonstrable.

The distinction between benign and malignant (essential) hypertension is worth further comment, for there has been some doubt in the past whether

they are the same disease, especially because of the earlier age incidence of the malignant type. In the present study the presence of papilloedema has been taken as the criterion on which a diagnosis of malignant hypertension has been made. This is always accompanied by a very high diastolic pressure, but may precede the development of renal insufficiency. Histologically the characteristic finding in malignant hypertension is fibrinoid necrosis of arterioles. Biopsy in Case 4 showed that papilloedema may develop before these 'malignant' changes are observed in the arterioles of the kidney. In the author's opinion there are five good reasons for thinking that malignant and benign hypertension are variants of one disease.

1 They have the same hereditary background. In the present series 75.4 per cent of cases of benign hypertension and 76.5 per cent of cases of malignant hypertension fell into hereditary Groups 1 and 2, although the malignant cases had a larger proportion in Group 2 and a smaller in Group 1 than the benign.

2 When cases of secondary hypertension are carefully excluded the discrepancy in age between the two types becomes less evident. In this series the average age of the malignant group was 47 years, that of the benign group 55 years. Allowing for the rapidity of the course in the former it is not surprising that these patients seek advice some eight years earlier in their life-history.

3 A transition from the benign to the malignant type can sometimes be observed. Cases 4, 16, and 18 are examples.

4 The experimental work of Goldblatt (1937) and Wilson and Byrom (1941) has shown that in animals the changes of benign or of malignant hypertension may be produced by the same process, namely, renal ischaemia, varying only in degree.

5 Secondary hypertension in man, for example, hypertension due to chronic pyelonephritis, may be seen either in the benign or the malignant form (Cases 91, 94, and 100 are illustrative), and the causation is presumably the same in each instance.

Terminology

Finally a plea might be made for a better terminology. The word 'benign' is a misnomer when applied to a disease which is frequently fatal, the adjective 'malignant', although expressive, is objectionable at the bedside. It is suggested that the terms 'simple' and 'compound' hypertension might be used in the same sense in which they are applied to the interest on a loan. The one term implies a steady but slow accumulation of effect. The other infers that each advance in the disease sets the process in motion at an increased speed. Thus Wilson and Byrom's (1941) concept of a vicious circle in malignant hypertension could be symbolized

Summary and Conclusions

1 Previous studies of the family histories of patients with hypertension have shown a hereditary factor in 76 to 86 per cent of cases.

2 Urological studies of hypertension have demonstrated a renal factor in 26 to 30 per cent of cases

3 The present paper attempts to combine these observations in order to determine whether the cases without a family history of hypertension are those in which the hypertension is secondary to some demonstrable urological disorder

4 Owing to the usual difficulties in studying human genetics and in relying on patients' statements, it is impossible to advance a proof, but the evidence is compatible with the hypothesis that essential hypertension is a hereditary disease conveyed as a Mendelian dominant with a rate of expression of more than 90 per cent

5 The great majority of cases of hypertension which do not conform to this rule are not essential hypertension at all, but are secondary to some renal or other cause

6 Pyelonephritis, when chronic nephritis is excluded, is the commonest cause of secondary (that is, non-essential) hypertension

7 Evidence is set out supporting the assumption that benign and malignant (essential) hypertension are varieties of one and the same disease

8 A plea is made for a change of nomenclature, and it suggested that the terms 'benign' and 'malignant' should be replaced by the adjectives 'simple' and 'compound', indicating in one case a slow and steady increase, and in the other a state in which the advances of the disease accelerate its speed of progress

The author wishes to acknowledge his gratitude to his colleagues both at the Manchester Royal Infirmary and at Withington Hospital for allowing him to study their cases, and his debt to the authors of the two books on human genetics referred to in the References

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ADDENDUM

Since this paper was written another 77 cases of hypertension have been seen and examined. Of these, 44 were diagnosed as essential hypertension, 29 of them giving a clear history of hypertension in one or both parents (family history Group 1). Six had a negative heredity (Group 4).

The remaining 33 cases were diagnosed as secondary hypertension, and of these no less than 20 had a negative family history (Group 4). The final figures for Table I are therefore as follows:

	Essential hypertension	Other hypertensives
Group 1	75	14
Group 2	16	7
Group 3	20	14
Group 4	11	36
	<hr/> 122	<hr/> 71

APPENDIX

Notes In all cases careful inquiry was made into any history suggestive of renal disease, and in particular of 'bladder trouble', in view of the importance of pyelonephritis
 An inquiry for pregnancy toxæmia was also made in all relevant cases For the sake of brevity the negative result of this inquiry is not usually reported Similarly, where papilloedema is not reported, it may be assumed to have been absent
 A diagnosis of benign hypertension was made when papilloedema was absent, renal function good, and there was no historical evidence of renal or other cause for the hypertension Such cases were not usually investigated by intravenous pyelogram

Group I Family History Strongly Suggestive of Hypertension

No	Sex	Age	Family history	Clinical condition	Comments and diagnosis
1	M	34	Father died apoplexy, 63, Father's brother same Mother alive, 76 2 brothers, 1 sister well	250/140 Rapidly downhill course, papilloedema and renal failure	Malignant hypertension (Confirmed post mortem)
2	M	58	Father died Bright's disease, 48 Mother died apoplexy, 78 1 brother, 2 sisters well	270/140 Urea clearance, 5°. No papilloedema, no renal history	Severe benign hypertension Post mortem—hypertension with severe renal damage Without histological evidence of malignant phase
3	F	47	Father died cerebral hæmorrhage, 62 Mother died stroke, 74 1 elder sibling stillborn No brothers or sisters living	260/130 No retinopathy	Benign hypertension
4	M	39	Paternal grandfather died cerebral hæmorrhage, 65 Father died drink, heart failure, and arteriosclerosis, 59 Mother living 1 sister well, 36	240/145 5 years' known hypertension Recent severe paroxysmal headache Papilloedema	Malignant hypertension (early) Biopsy (during sympathectomy) = benign hypertension (see text)
5	F	43	Father known to have had low blood-pressure Mother died Bright's disease, 54 Mother's brother same, 46 (Both had high blood pressure) 1 brother died bacterial endocarditis, 36	225/145 Papilloedema Retinopathy	Malignant hypertension (confirmed by biopsy)
6	F	51	Father had hypertension, died stroke, 67 Paternal grandmother same	210/120 No retinopathy Hypertension known 6 years	Benign hypertension
7	F	69	Father died cancer, 56 Mother died stroke, 49 2 brothers well 1 brother died fits, 32	220/100 (Treated for 'blood pressure' 2 years)	Benign hypertension (Carcinoma of stomach)

8	M	52	Father died heartstroke (Basal), 52 years and died, 62 2 younger sisters well	200/120 Cardio symptoms Norotino. Benign hypertension	
9	F.	50	Father died asthma and bronchitis, 50 Elder sister has carcinoma of colon, 48 sister, 2 brothers well	220/110 History of renal calculus No papilloedema	
10	F	53	Father died apoplexy, 60 83 1 older, 1 younger sister well	No Benign hypertension	Renal calculus
11	F	57	Father died heart and kidney trouble, died blood poisoning, 82 1 sister septic poisoning 1 sister died seizure 1 brother, 1 sister has had a No such history on mother's side	225/130 Angina Heart failure Renal pain, frequency, scalding Urine nega- nophritis	Benign hypertension ? Healed pyelo
12	M	44	Father died hypertension and kidney, 60 Mother has hypertension, 74 Sister 160) Sister anaemia, 30	200/112 No papilloedema	Benign hypertension
13	M	42	Father died suddenly (collapsed in street), 53 Mother well, 64 Brother died confinement, 23	220/110 " "	(Severe) benign hypertension (confirmed by biopsy)
14	F	70	Father died seizure (suddenly), 81 Mother died several seizures, 67 Sister died suddenly (2 or 3 seizures), 1 brother, 1 sister, unknown 4 other siblings died in childhood	220/100 No retinopathy Recent he manopia (probable cerebral throm- bosis)	" "
15	M	51	Father died heart failure, 61 Mother died cerebral haemorrhage, 67 No siblings	210/110 Cerebral haemorrhage	Benign hypertension
16	M	50	Father died stroke, 63 Paternal grand- father the same 1 older brother quite well	250/130 Hypertension known since 62 Papilloedema.	" "

Group I (continued)

No	Sex	Age	Family history	Clinical condition	Comments and diagnosis
17	M	46	Father died suddenly (heart), 72 Mother 'has blood-pressure', 75	210/110 (218/110 six years ago) symptoms	Benign hypertension
18	F	58	Father died cancer, 60 cerebral haemorrhage, 69 brothers Only 5 grew up 2 suicides, 1 typhoid, 1 died kidney and high blood pressure, 54	280/135 Papilloedema Recent dysphasia Slight homoplegia 5 years ago Urea clearance 68 %	Essential hypertension (becoming malignant)
19	F	42	Father died 'bronchitis' (opistaxis, dyspnoea, rapid loss of vision), 65 Mother alive, 71 1 elder sister died meningitis, 17 5 younger siblings living	270/140 (later 170/120) No papilloedema No renal history	Benign hypertension
20	F	76	Father died, cause unknown, 85 Mother died heart, 50 1 brother died heart and kidneys, 78 1 sister died diabetes, 65 1 sister died heart, 60 1 sister died cancer, 77 1 sister died stroke, 79 1 sister well, 78 Daughter blood-pressure 130/80, 46 Son died accident, 10	200/100 Known hypertension 14 years Recent cerebral thrombosis	" "
21	F	57	Father died tuberculosis, 53 Mother died high blood pressure, 61 lungs 1 daughter well	210/120 Papilloedema Retinopathy	Malignant hypertension
22	F	35	Father died cancer Mother died stroke, 7ago 1 brother died accident 1 sister died stroke, 43 1 sister alive, rheumatic heart	200/145 Papilloedema Retinopathy 2 years ago frequency, backache, haematuria, 1 year ago (4 months pregnant) headache, hypertension, oedema (pregnancy terminated)	Malignant hypertension ? Healed pyelonephritis
23	M	58	Father died carcinoma of stomach, 58 Mother alive, 87 1 brother alive, hypertension, 64 1 brother died hypertension, 61 2 brothers killed in action (1914-18)	210/125 Left ventricular failure History, trench nephritis, 1917 No sequelae	Benign hypertension
24	F	71	Father died young, cause unknown Mother died 71 Had stroke at 70 1 brother alive, 80 1 sister died, cause unknown, 76	250/120 Angina	" "

Group I (continued)

No	Sex	Age	Family history	Clinical condition	Comments and diagnosis
17	M	40	Father died suddenly (heart), 72 Mother 'has blood pressure', 75	210/110 (218/110 six years ago) Few symptoms	Benign hypertension
18	F	58	Father died cancer, 60 cerebral haemorrhage, 69 brothers Only 5 grew up 2 suicides, 1 typhoid, 1 died kidney and high blood-pressure, 54	280/135 Papilloedema Recent dysphasia Slight hemiplegia 5 years ago Urea clearance 68%	Essential hypertension (becoming malignant)
19	F	42	Father died 'bronchitis' (epistaxis, dyspnoea, rapid loss of vision), 65 Mother alive, 71 1 older sister died meningitis, 17 5 younger siblings living	270/110 (later 170/120) No papilloedema No renal history	Benign hypertension
20	F	70	Father died, cause unknown, 85 died heart, 50 1 brother died heart and kidneys, 78 1 sister died diabetes, 65 1 sister died heart, 60 1 sister died cancer, 77 1 sister died stroke, 79 1 sister well, 78 Daughter blood pressure 130/80, 40 Son died accident, 10	200/100 Known hypertension 14 years Recent cerebral thrombosis	" "
21	F	57	Father died tuberculosis, 53 died high blood pressure, 61 No siblings 1 daughter well	210/120 Papilloedema Retinopathy	Malignant hypertension
22	F	35	Father died cancer Mother died stroke, 7 age 1 brother died accident died stroke, 43 1 sister alive, rheumatic heart	200/145 Papilloedema Retinopathy 2 years ago frequency, backache, haematuria, 1 year ago (4 months pregnant) headache, hypertension, oedema (pregnancy terminated)	Malignant hypertension ? Healed pyelonephritis
23	M	58	Father died carcinoma of stomach, 58 Mother alive, 87 1 brother alive, hypertension, 64 1 brother died hypertension, 61 2 brothers killed in action (1914-18)	210/125 Left ventricular failure History, trench nephritis, 1917 No sequelae	Benign hypertension
24	F	71	Father died young, cause unknown Mother died 71 Had stroke at 70 1 brother alive, 80 1 sister died, cause unknown, 76	250/120 Angina	" "

14	F	64	Father died intestinal obstruction, 76 Mother died kidney trouble and heart, 46 Sister died suddenly, 46 Brother living	180/110 Diabetes and heart failure Blood urea 38	Benign hypotension (Diabetes)
15	F	42	Father died enemy action Mother died stroke, 19 1 older, 3 younger siblings living	230/140	Severe benign hypertension
16	F	50	Father living, 75 Mother died seizures and heart, 74 No siblings	190/110	Benign hypertension
17	F	35	Father died, 70 Kidney trouble ('poly- cystic') Mother living, 67	180/110	Double kidney left with hydropnephrosis Split pelvis right
18	M	47	Father died 'blood pressure', 75 Mother died influenza, 57 2 older, 5 younger siblings living	190/110 Ménière's syndrome	Benign hypertension
19	F	52	Father died stroke, 80 Mother died stroke, 69 2 sisters and 3 brothers living (Brother has frequent epistaxis)	195/110 Obesity	" "
50	F	15	Father died corobral haemorrhage, 56 Mother living, 75 Brother died pneu- monia, 18 Sister living	230/100 'Weak bladder since child- hood' Albumin 4 gm %, pyuria, cul- ture sterile Urea clearance 32 %	Chronic pyelonephritis
51	F	63	Father died pernicious anaemia, 81 Mother died heart and high blood pres- sure, 71 No siblings	260/130 Cardiac symptoms	Benign hypertension
52	F	44	Father well, 72 Mother died stroke, 65 1 siblings (1 older) living	270/150 Albumin + Papilloedema Urea clearance 80 %	Malignant hypertension
53	M	54	Father died cerebral haemorrhage, 65 Mother died bronchitis and heart, 70 1 brother, 1 sister living	235/170 Dilated heart Gallop rhythm No papilloedema	Severe benign hypertension
54	F	43	Father died cancer and stroke, 60 Mother living has high blood pressure, 63 1 sibling living	250/125 No papilloedema Albumin + Urea clearance 45 % Previous history of cystitis	Chronic pyelonephritis
55	M	10	Father died heart, 39 Mother died heart, 63 1 brother, 1 sister well 1 sister died young	195/125 Early papilloedema	Malignant hypertension

Group II Family History Probably Indicates Hypertension

Group I (continued)

No	Sex	Age	Family history	Clinical condition	Comments and diagnosis
35	F	48	Father died seizure, 74 Mother living (rheumatism), 78 1 brother died suddenly (heart), 48 3 older, 2 younger siblings, well 2 died in infancy	240/130	Benign hypertension
36	F	67	Father died accident, 37 Mother died, cause unknown, 57 1 sister died stroke, 47 1 sister died accident 2 brothers died, cause unknown	245/160 Cardiac symptoms	"
37	M	51	Father died accident, 68 Mother died Bright's disease and high blood-pressure, 48 3 older siblings living 3 died (diabetes, cancer, unknown)	210/105 Left hemiplegia	"
38	F	65	Father died (headaches, blindness, coma), 70 Mother died gallstones, 80 Eldest of 6 (1 died accident)	190/110	"
39	M	56	Father died seizure, 76 Mother died, cause unknown, 42 2 older, 2 younger siblings living 1 sister died nephritis, 17	220/120	"
40	M	52	Father died cancer of throat and heart disease, 71 Mother died cancer of stomach, 50 1 brother died wounds 1 sister hypertension, 58 1 brother living, 62	225/145 (175 eight years ago)	"
41	F	50	Father died angina, 52 Mother died heart (suddenly), 79 Sister 'blood-pressure', 58 Brother angina and diabetes, 56 Brother died ulcer, 44 Brother died accident, 9 3 younger siblings well	196/100 Cardiac symptoms	"
42	F	47	Father died seizure, 64 Mother died heart, 57 2 older brothers living 1 sister died pneumonia	196/104 Pyelonephritis 10 years ago	† Pyelonephritis
43	M	48	Father, fate unknown Mother died young, † cause 1 older sister 'blood-pressure' 2 older sisters living	210/125 Cardiac symptoms Recent hemiplegia	Benign hypertension

67	F	56	Father died chill, 70 Mother died suddenly heart, 58 (her mother same, 63) 7 siblings (2 older), 1 died heart	250/145 Pregnancy toxæmia 24 years ago, no sequelæ Recent acute nephritis (throat, swollen face, hæmaturia) No albumin now Urea clearance 100%	Probable benign hypertension
68	M	51	Father died suddenly heart Mother died, 1 cause, 10 1 older sister died, 1 cause 1 younger sister living	225/100 Has worked in lead heart block Renal function normal	Doubtful ? Lead poisoning
69	M	42	Father died cancer, 75 Mother died heart, 73	186/124 Cardiac symptoms Diarrhoea and swelling of face 6 months ago No albuminuria	Probable benign hypertension
70	F	30	Father died heart (sudden), 50 well	240/140 Cystitis 4 years ago Pelvic operations Urea clearance 52% Intravenous pyelography - deformity left Urine sterile	Chronic pyelonephritis
71	F	44	Father died suddenly heart, 38 died cancer, 70 No siblings	250/150 Papilloedema Intravenous pyelography normal	Malignant hypertension
72	F	65	Father died suddenly, 56 old age, 78 1 sister died coronary disease, 72 1 brother died, 1 cause, 74 1 brother living, 70	270/175 Cardiac failure	Severe benign hypertension
73	M	70	Father died accident, 48 old age, 84 1 brother died, 1 cause, 50 2 sisters well	186/126 Heart failure	
74	M	26	Father well Mother died pneumonia, 40 Half-brother died pneumonia, 3	215/160 Papilloedema, pyrexia, abdominal pain, leucocytosis, etc	Benign hypertension
75	F	55	Father died cancer, 56 old age, 70 1 older, 1 younger siblings	200/100 Thyroidectomy 3 years ago	Periarteritis nodosa (confirmed by autopsy)
76	M	63	Father died suddenly, 1 cause, 70 Mother died cancer, 73 1 older, 1 younger sibling living	180/120 Hypertension known 7 years No retinopathy Urea clearance 68%	? Benign hypertension.
77	M	52	Father died cerebral trouble, 60 died, 1 cause, about 30	180/110 Angina	Benign hypertension
78	F	45	Father died, cause unknown, 50 died childbirth, 30 +	226/130	" "

Group III Family History Incomplete

Group II (continued)

No	Sex	Age	Family history	210/136	Clinical condition	Comments and diagnosis
56	M	40	Father well, 74 Mother died heart, 69 1 older sister well 6 brothers, 2 sisters younger	urinary infection graphy normal	History of intravenous pyelo- nephritis	Malignant hypertension (biopsy during sympathectomy does not show pyelo- nephritis)
57	M	45	Father living, said to have 'kidney disease', 67 Mother well 6 younger brothers and sisters 2 died in child- hood	220/130 No retinopathy		Benign hypertension (severe) (confirmed by biopsy)
58	F	49	Father died suddenly, 62 Mother died old age, 70 2 older, 5 younger siblings living	250/110 (210/110, 3 years ago) No re- tinopathy 3 normal pregnancies		Benign hypertension
59	F	48	Father died carcinoma of bladder, 73 (thought to have had 'blood pressure') Mother living, 76 1 older, 1 younger brother living	220/130 Subarachnoid haemorrhage Similar attack 9 years ago Papil- oedema improving		? Benign hypertension ? Cerebral cause
60	M	56	Father died, 7 cause, 68 Mother died dropsy, 62 No siblings	285/180 Papilloedema and retinopathy Blood urea, 106		Malignant hypertension (confirmed by autopsy)
61	M	48	Father died some cerebral condition, 55 Mother died cancer, 44 3 siblings (2 younger) living	230/150 Papilloedema Blood urea, 92 No renal history		Malignant hypertension
62	F	52	Father died accident, 75 Mother died heart, 65 2 younger brothers living	220/130 Cardiac symptoms		Benign hypertension
63	F	43	Father died coronary occlusion, 70 His sister and brother same at 60 and 50 + Mother well, 80 1 sister (a doctor), 41	210/110 Hypertension known 7 years		" "
64	F	54	Father died heart, 71 Mother died heart, 47 2 older brothers well	250/160 No retinopathy Hemiplegia		" "
65	F	38	Father died tuberculous kidney, 41 Mother has duodenal ulcer, 68 1 bro- ther, age 34, blood pressure, 165 (pa- tient's statement)	255/140 No retinopathy Hypertension known 8 years No renal history No pregnancy		Benign hypertension (severe) (confirmed by biopsy)
66	F	37	Father died heart following asthma, 40 Mother alive and well 2 sisters (1 en- cephalitis, 1 gall stones)	250/160 Papilloedema Urea clearance 63 %		Malignant hypertension

90	F	65	Father died old age, 84 childbirth, 46 Brother died cancer 2 younger siblings living	200/110 (200/120 3 years ago)	Benign hypertension
91	M	38	Father died accident, 35 ? cause, 68 3 older, 2 younger siblings living	250/140 No papilloedema 38 Urea clearance 92 History of pye- lonephritis	Chronic pyelonephritis (confirmed by biopsy)
92	M	63	Father died, ? cause, 19 phlebitis, 54 4 siblings died, cause un- known 3 siblings living	180/120 Auricular fibrillation	Benign hypertension
93	M	51	Father died influenza, 50 old age, 70 Brother, 65, sister, 61, sister, 50, living	200/110 Trench nephritis 28 years ago. No sequelae	Probable benign hypertension
94	F	60	Father died young 70 1 younger brother	250/135 Repeated Atrophic kidney right	Chronic pyelonephritis (confirmed by nephrectomy)
95	M	72	Father died pneumonia, 43 died strangulated hernia, 45 8 older siblings (eldest 45) living	170/115 Frequency, dysuria, history of urinary infection Refused admission	? Chronic pyelonephritis
96	F	50	Father died cancer, 57 gallstone, 74 2 sisters, 4 brothers living	<i>Group IV No Family History of Hypertension</i> 200/125 Repeated pain right loin Double ureter right and left	Congenital renal abnormality
97	F	35	Father well, 67 Mother well (has had pelvic operations, 65) 1 brother, 39, well (Parents unable to attend for examination)	230/120 No papilloedema No pre- nancy Intravenous pyelography nor- mal	Benign hypertension Biopsy right and left shows occasional glomerular sclero- sis No histological evidence of hyper- tension
98	F	54	Father living, 82 Mother died old age, 76	230/140 Papilloedema Blood-urea 100 History of pyelonephritis	Chronic pyelonephritis
99	M	50	Mother died old age, 70 Father died pneumonia, 64 2 sisters died in infancy	210/150 Papilloedema Heart failure Blood urea 74 Clearance 35% Albu- min ++	Malignant hypertension (Died at home No autopsy)
100	F	31	Father and mother alive and well No siblings	200/150 Papilloedema Terminal urae- mia Cystitis at 7 years Frequently since	Chronic pyelonephritis (confirmed at autopsy, hypoplastic left kidney)

Group III (continued)

No	Sex	Age	Family history	Clinical conditions		Comment and diagnosis
				No retinopathy	Hemiplegia	
79	F	70	Father died tuberculosis, 29 died senility, 83 1 brother died pros- tato, 68 1 brother living (prostate), 67 1 younger sister living	220/120		Benign hypertension
80	F	39	Mother died encephalitis, 42 alive, diabetes No hypertension in sib lungs	220/120	Followed pregnancy toxæmia	Pregnancy toxæmia
81	M	55	Father died heart (rheumatic), 35 Mother living, 77 1 younger brother living	274/160	Papilloedema	Malignant hypertension
82	M	62	Father died cause unknown, 58 died pernicious anaemia, 73 1 older, 1 younger sibling living	220/104	Coronary occlusion	Benign hypertension
83	F	51	Father died cancer, 48 1 brother, 2 sisters, and niece died of Lindau's disease 1 brother died acci- dent	190/100	Typical polycystic kidneys (X-ray, etc)	Polycystic kidney
84	M	68	Father died, 1 cause, 78 bronchitis, 80 Brother and sister, 71 and 65, living 1 brother died heart, 61	210/100	Cardiac symptoms	Benign hypertension
85	M	55	Father died, 1 cause, 71 young, 1 cause 2 brothers killed in action 1 sister living	230/100	(200/100, two years ago) Cardiac symptoms	" "
86	M	50	Father died young, 1 cause died, 1 cause, 43 Brother died pneu- monia 2 younger sisters living	200/120	Hemiplegia	" "
87	F	73	Father died pneumonia, 50 died bronchitis, 78 Brother died sud- denly, 77 1 brother, 1 sister died, cause unknown	220/110	Auricular fibrillation	" "
88	F	58	Father killed in air raid, 70 died young 1 brother, 1 sister living	250/170	Urinary infection 5 years ago Urine sterile No papilloedema	Severe benign hypertension or pyelo- nephritis
89	M	41	Father and mother died 'when he was a boy' No siblings	240/160	Papilloedema Heart failure	Malignant hypertension

			Typical polycystic kidneys	Polycystic kidney
		225/130	Became normal on resting in (X-ray, etc)	Benign hypertension (minimal)
M	46	Father died old age, 73 and well, 75 2 older, 6 younger sibs living	170/105 Hospital	Post mortem (at another hospital), kidneys macroscopically normal—carcinoma of bronchus
M	35	Father died cancer, 56 3 older, 2 younger sibs living	194/110 Albuminuria ++	Diagnosis doubtful
F	55	Father died cancer, 65 2 older, 2 younger sibs living	several times	Diagnosis doubtful
		200/120 Cardiac failure, 5 years repeated pain left loin	Haematuria	
M	58	Father died at sea, 60 pneumonia, 62 1 older, 3 younger sibs living 3 killed in action	albumin ++	
			pyelography	
			Left kidney not well defined	
			Hypertension known 4 years	
			Recent left hemiplegia	
			Severe abdominal pain	
			No papilloedema	
			Recent left hemiplegia	
			Obesity, kyphosis, hirsutism, epileptiform attacks, hyperostosis frontalis interna	
			Nocturia and polyuria since childhood	
			Papilloedema and exudates	
			Frequency and scalding	
			X-ray—renal calculus and deformed pelvis right	
			Renal calculus, etc	
			Chronic pyelonephritis	
			Hyperostosis frontalis (Morgagni's syndrome)	

Group IV (continued)

No	Sex	Age	Family History	Clinical condition	Comments and diagnosis
101	M	47	Father died old age, 91 Mother died, 75 10 older siblings, 5 well ? cause, 75 10 older siblings, 5 well 2 killed in action 3 died (pneumonia, asthma, childbirth)	200/120 History of pyelonephritis 13 years ago Intravenous pyelography normal Blood urea 38	? Chronic pyelonephritis
102	F	52	Father died cancer, 72 Mother died arteriosclerosis, 86 No siblings	200/110 3 attacks of cystitis following operation for carcinoma of rectum In- termittent pain right kidney Urino- sterile Intravenous pyelography failed	Chronic pyelonephritis
103	F	39	Father living (duodenal ulcer), 68 Mother well, 65 1 brother duodenal ulcer 1 sister well	200/130 Hypertension developed during prolonged pyrexial illness with nodules, rheumatic pains, etc Biopsy for peri- arteritis doubtful	Periarteritis nodosa
104	M	46	Father died 'chill', 75 Mother died same, 75 5 older, 2 younger siblings (1 killed in action)	190/110 Haematemesis (duodenal ul- cer), 23 years ago 'chill on kidneys' (backache and dysuria), minor attacks since	Chronic pyelonephritis
105	M	50	Father living, 76 Mother living, 70 9 younger siblings (2 died young)	230/145 Papilloedema Recent haema- turia Intravenous pyelography nor- mal	Malignant hypertension
106	M	45	Father died pneumonia, 62 Mother alive and well 1 brother, 1 sister living	280/150 Papilloedema and exudates Blood urea 48 Clearance 54%. Intra- venous pyelography No excretion right or left 2 calculi right kidney, 1 calculus left kidney	Renal calculus
107	F	41	Father and mother alive and well	290/160 Terminal uraemia, pyrexia, raised swollen red skin lesion of face Post mortem—endocarditis and un- certain renal pathology (not lupus erythematosus)	? Bacterial endocarditis
108	F	30	Father living, 70 Mother living—di- betes, fatty heart, used to be obese 3 older, 2 younger siblings living Mother not available for examination	210/110 Extreme obesity (18 stone), not Cushing type	Benign hypertension Obesity

THE SIGNIFICANCE OF THE VAN DEN BERGH REACTION¹

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Introduction

A REASSESSMENT of the clinical significance of the van den Bergh reaction is rendered highly desirable by the development during the last 15 years of new methods for the determination of bilirubin in body fluids as well as for the estimation of the proportions of the alleged direct and indirect forms of bilirubin. Moreover, modern photo-electric devices permit an accurate measurement of the rate of formation of colour in the van den Bergh diazo reaction, and thereby offer a more objective means of distinguishing between so-called prompt, biphasic, and delayed direct van den Bergh reactions given by jaundiced sera. Van den Bergh and Muller (1916) showed that the presence of alcohol was not necessary in the production of the red pigment azobilirubin by the action of a solution of diazotized sulphanilic acid (the Ehrlich diazo reagent) on bile or sera from patients with obstructive² (regurgitation) jaundice. Such sera were said to give a direct reaction in contrast to sera from normal persons or from patients with haemolytic (retention) jaundice, which formed azobilirubin with the diazo reagent only in the presence of alcohol or other hydroxylic substances, and which were said therefore to give an indirect reaction. Van den Bergh and Muller (1916) observed that sera giving the indirect reaction either completely failed to react with the diazo reagent in the absence of alcohol, or gave only a delayed direct reaction, but they did not regard these differences as of clinical significance. Later workers (Feigl and Querner, 1919, Lepehne, 1920, McNee, 1922) subdivided the direct reaction into prompt and biphasic types according to whether the formation of azobilirubin rapidly approached its maximum or whether the initial period of rapid formation was followed by a more gradual deepening of the colour. Such biphasic reactions, which are common in hepatogenous jaundice, have hitherto been regarded as due to the presence in the serum of two forms of bilirubin, one (direct bilirubin) giving a prompt reaction, and the other (indirect bilirubin) the delayed reaction characteristic of retention jaundice. Attempts to determine the rate of formation of azobilirubin in the direct reaction have been made by Malloy and Evelyn

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² In the present article the nomenclature used will be that of Rich (1930) who classified jaundice into retention and regurgitation types. Retention jaundice corresponds to haemolytic jaundice, but regurgitation jaundice is subdivided into mechanical and parenchymal types corresponding to obstructive and hepatogenous jaundice respectively [Q.J.M. New Series No. 63]

is no longer tenable. Moreover, the existence of two distinct forms of bilirubin has never been demonstrated unequivocally, so that the significance of alleged measurements of direct and indirect bilirubin requires reinterpretation. Methods of investigation depending on the alleged solubility in chloroform of indirect bilirubin are useless owing to incomplete extraction in the presence of protein, and need no further consideration. Measurements of the relative proportions of azobilirubin formed with and without the addition of alcoholic substances might be more satisfactory, and Gray and Whidborne (1947) have suggested that the use of the terms direct and indirect bilirubin should be abandoned in favour of the term direct-indirect quotient. This direct-indirect quotient, conveniently abbreviated to D I Q, may be defined as

$$\frac{\text{final amount of azobilirubin formed in the direct reaction}}{\text{final amount of azobilirubin in the indirect reaction}} \times 100$$

It has long been known that sera from patients with retention jaundice may give delayed direct van den Bergh responses, and since similar reactions may be obtained in regurgitation jaundice as well as chronic liver damage when the serum-bilirubin is only slightly raised, it appeared important to investigate more fully the possibility of distinguishing these conditions by determination of the rate of the direct reaction, or by suitable measurements of D I Q. The value of D I Q will vary with the pH at which the reaction is investigated and with the time at which the extent of the direct reaction is measured, as well as with the composition of the reaction mixture of the particular method used. The problem therefore presents itself as to which of the various methods of measuring D I Q is of the greatest value in clinical work.

Methods

Of the methods available, only those are worthy of consideration in which the risk of adsorption of pigment on to precipitated protein is avoided. The methods of Rappaport and Eichhorn (1943) and Malloy and Evelyn (1937) fulfil this condition, and it has been shown that for the determination of total bilirubin these two methods agree well, provided precautions are taken in the preparation of the calibration curves. The direct reaction was investigated by a photo-electric modification of the method of Rappaport and Eichhorn, the course of the direct reaction being followed by measuring the azobilirubin formed after varying times in the presence of a phosphate buffer containing urea. Since with certain sera the presence of urea in the reaction mixture has a profound effect upon the course of the direct reaction,³ similar investigations have been made using a phosphate buffer without urea. Similarly, the course of the indirect reaction was followed by measuring the azobilirubin formed after varying times in the presence of a buffer containing

³ The final concentration of urea in the reaction mixture is 18.6 gm per 100 c.c. and the effect described above is not seen when urea is present in the much smaller concentrations found in the body fluids in clinical uraemia.

(1937), Lepelne (1941), and Gray and Whidborne (1946) in order to distinguish between prompt, biphasic, and delayed direct van den Bergh reactions

Numerous methods of determining the proportion of directly and indirectly reacting bilirubin have therefore been described, some depending on an alleged difference in solubility in chloroform of the two forms of bilirubin (Newman, 1928, Sepulveda and Osterberg, 1942) Ducci and Watson (1945) have shown that the chloroform-soluble bilirubin is regularly less in amount than the indirect bilirubin fraction as determined by another procedure, and it seems reasonably certain that a variable loss of bilirubin must result when attempts are made to extract the pigment in the presence of protein. Others have measured the relative proportions of azobilirubin formed with and without the addition of alcoholic substances. Malloy and Evelyn (1937) compared the amount of azobilirubin formed in aqueous solution in 30 min with the total amount formed in the presence of methyl alcohol. Rappaport and Eichhorn (1943) measured so-called direct bilirubin by azobilirubin formation in the presence of a phosphate buffer containing urea, and total bilirubin in the presence of citric acid and caffeine. Ducci and Watson (1945) differentiated prompt-reacting bilirubin and delayed direct-reacting bilirubin by measuring the azobilirubin formed in 1 min and 15 min under the conditions of the Malloy and Evelyn method. It therefore appears necessary to consider critically the relative merits of each of these methods of investigation, and to decide which, if any, are likely to be of greatest value in clinical diagnosis.

Prompt, Biphasic, and Delayed Reactions and their Clinical Significance

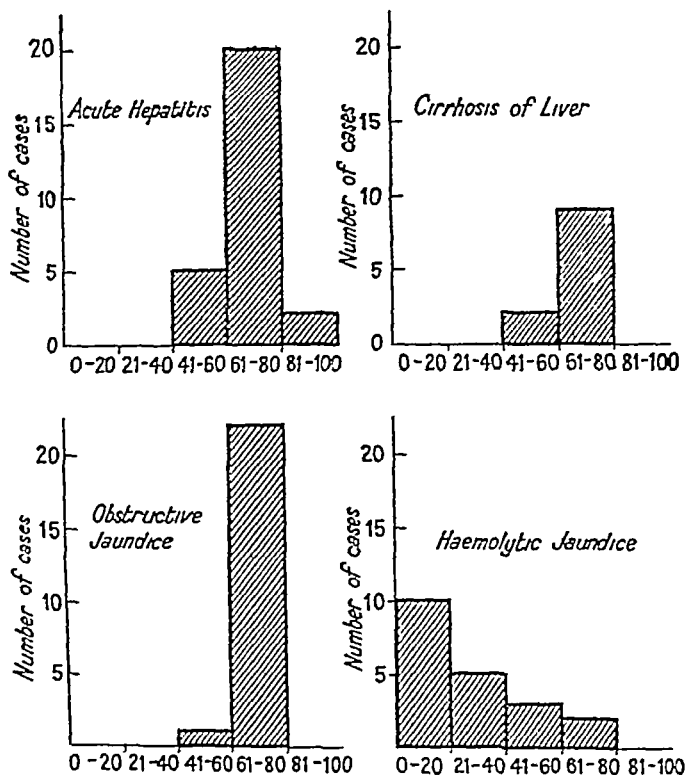
A photo-electric method for investigating the direct van den Bergh reaction by following the rate of formation of the red pigment was first described by Malloy and Evelyn (1937). Lepelne (1941), however, found this method to be of little value in diagnosis. Gray and Whidborne (1946) used a modification of the method of Rappaport and Eichhorn (1943) and followed the course of the direct reaction by measuring the azobilirubin formed after varying times. It was thus shown that sera from patients with acute hepatitis or obstructive jaundice gave a prompt, biphasic, or delayed reaction according to the amount of bilirubin present and not according to the type of jaundice. These different appearances were found to be due to the failure of strong azobilirubin solutions to absorb light proportionately to their concentration (that is, they fail to obey Beer's Law). The classification of direct van den Bergh reactions into prompt, biphasic, and delayed types is therefore of no value whatever in the differentiation of acute hepatitis from obstructive jaundice.

The Direct-Indirect Quotient (D I Q)

The biphasic reaction given by some sera was formerly attributed to the presence of both direct and indirect reacting bilirubin, but this explanation

usually observed, while the D I Q was generally much lower than in regurgitation jaundice. In one case of retention jaundice, however, the direct reaction in the absence of urea was rapid on three different occasions, and the D I Q was well within the limits found for regurgitation jaundice.

The course of the indirect reaction The indirect reaction was rapid in all



The direct-indirect quotient of jaundiced sera

cases of regurgitation jaundice examined, but in retention jaundice it was slow in about two-thirds of the cases.

These results are summarized in Table I.

Malloy and Evelyn method Table II shows the D I Q values given by the Malloy and Evelyn method when measurements were made at 1, 15, and 30 min. after the addition of the diazo reagents. The Figure shows the distribution of 30 min. D I Q values found in cases of acute hepatitis, obstructive jaundice, haemolytic jaundice, and cirrhosis of liver.

Discussion

The visual direct van den Bergh reaction It is generally recognized that the ordinary direct van den Bergh reaction is of only limited value in diagnosis. A delayed direct reaction is often seen with sera from patients with retention jaundice partly owing to the frequent coexistence of liver damage, and

caffeine and sodium citrate. Measurements by the Malloy and Evelyn method were made at 1, 15, and 30 min after mixing the reagents. These investigations have been described in detail elsewhere (Gray and Whidborne, 1946, 1947). All measurements of azobilirubin were made in the Spekker photo-electric absorptiometer.

Results

Rappaport and Eichhorn method A detailed analysis of most of the results has been given elsewhere, but for clinical purposes the direct reaction may

TABLE I

The Nature of the Diazo Reactions and the Direct-Indirect Quotient (D I Q) of Sera in Regurgitation and Retention Jaundice

	Type of jaundice	Speed of reaction	Number of sera	D I Q
Direct reaction in presence of urea	Regurgitation	Rapid	42 (33 cases)	79 ± 1.6 (57-100)
	Retention	"	59 (30 ")	79 ± 1.3 (59-100)
	"	Slow	6 (5 ")	53 ± 6.1 (30-74)
Direct reaction in absence of urea	Regurgitation	Rapid	12 (9 cases)	75 ± 1.6 (68-84)
	Retention	Slow	11 (9 ")	35 ± 5.6 (8-78)
	"	Rapid	3 (1 case)	67, 69, and 71
Indirect reaction	Regurgitation	"	42 (33 cases)	—
	Retention	Slow	41 (33 ")	—
	"	Rapid	22 (13 ")	—

TABLE II

D I Q Values Obtained at 1, 15, and 30 Minutes by the Malloy and Evelyn Method

	Type of jaundice	Number of sera	D I Q
1 min reading	Regurgitation	12	32 ± 1.6 (34-41)
15 " "	"	12	61 ± 1.3 (55-69)
30 " "	"	12	65 ± 1.0 (60-71)
1 " "	Retention	6	23 ± 1.2 (0-9)
15 " "	"	6	11 ± 1.6 (8-16)
30 " "	"	16	30 ± 5.4 (8-69)

be described as rapid when it is 90 per cent complete within 30 min, and slow when it is not. These terms have been used in preference to the more usual prompt and delayed direct reaction, because there is no correlation between the diazo reaction in the presence of urea and the ordinary van den Bergh reaction.

Urea present in the reaction mixture In regurgitation jaundice the direct reaction was always rapid, and the D I Q high, that is, above 55. With 59 sera from 30 cases of retention jaundice the D I Q was equally high and the direct reaction rapid, whereas it was slow in only six sera from five cases of retention jaundice. In the last six sera the D I Q was significantly lower than that encountered with sera from cases of regurgitation jaundice.

Urea not present in the reaction mixture In regurgitation jaundice the direct reaction was just as rapid and the D I Q just as high as was found in the presence of urea. In retention jaundice a slow direct reaction was

always, lower than in regurgitation jaundice. The series of cases of chronic liver damage examined by the Malloy and Evelyn technique gave, as was expected, similar results to those observed in regurgitation jaundice.

Conclusions

It is clear that even with the refined modifications of the van den Bergh reaction now available, it is impossible to distinguish between the parenchymal and mechanical forms of regurgitation jaundice, and it is not always possible to distinguish with certainty between retention and regurgitation jaundice. Retention jaundice is frequently complicated by liver damage and in such circumstances can be distinguished from regurgitation jaundice only by more elaborate hepatic function tests. It is possibly worthy of mention that in one case of constitutional non-haemolytic jaundice the typical findings of retention jaundice were observed, although it is generally considered that the inability of the liver to clear bilirubin is the principal factor in the causation of this condition.

Of the methods studied, the Malloy and Evelyn measurement of D I Q at 30 min is the simplest and most helpful. The Malloy and Evelyn method is specially valuable since it gives more accurate results for the determination of total bilirubin than most of the earlier methods. A D I Q below 40 is diagnostic of retention jaundice, and a D I Q above 50, although usually indicative of regurgitation jaundice, can occur in retention jaundice complicated by liver damage. A D I Q between 40 and 50 is highly suggestive of, but not absolutely diagnostic of, retention jaundice. In cases of difficulty a reticulocyte count, erythrocyte fragility estimation, search for spherocytosis, or determination of the faecal stercobilin excretion may be essential for the clinician to establish the diagnosis.

Summary

1 The significance of the various types of direct van den Bergh reaction is discussed, and it is emphasized that the so-called biphasic reaction is not due to the presence in the serum of two forms of bilirubin, but to the failure of strong solutions of azobilirubin to follow Beer's Law.

2 The terms direct and indirect bilirubin should be abandoned because there is no proof that these two forms really exist.

3 The use of the term direct-indirect quotient (D I Q) is recommended since it merely gives an expression of the extent of the direct reaction under the conditions of the experiment.

4 Neither the direct van den Bergh reaction nor any of its modern modifications enable one to distinguish between the jaundice of acute hepatitis and that due to obstruction.

5 For clinical purposes, the method of Malloy and Evelyn is the simplest and best of those examined. A D I Q below 40 is then diagnostic of retention jaundice, and a D I Q above 50, although usually indicative of

partly because a weak direct reaction is very readily detected since the serum is only diluted with half its volume of diazo reagent. With considerable experience of the visual van den Bergh reaction, it is possible to judge with a fair degree of accuracy whether a given delayed direct reaction is likely to be associated with regurgitation or with retention jaundice if it is considered in relation to the total amount of bilirubin present. Thus the direct reaction associated with a total serum bilirubin of 2.0 mg per 100 cc in regurgitation jaundice, may be stronger than that observed with a total bilirubin of 4.0 mg per 100 cc in retention jaundice. Such distinctions are difficult and may be misleading when the retention jaundice is accompanied by liver damage.

The Rappaport and Eichhorn method and its modifications. The rapid rate of the direct reaction in the presence of urea observed in almost all cases of jaundice clearly renders such investigations useless for the differentiation of retention from regurgitation jaundice. In the absence of urea the slow reaction and significantly lower D I Q in retention jaundice suggest that such investigations might be of greater value, but the occasional occurrence of a rapid reaction and a high D I Q in such cases limits the significance of these findings. The considerable percentage of rapid indirect reactions in retention jaundice similarly limits the value of following the course of the indirect reaction. Thus a slow indirect reaction is almost diagnostic of retention jaundice, but a rapid indirect reaction may occur in either retention or regurgitation jaundice. It is probable that such determinations of the rate of formation of azobilirubin give no less information than do the D I Q determination at 30 min by the Malloy and Evelyn method. The infinitely greater rapidity and simplicity of this latter method, however, renders it unquestionably the method of choice.

The Malloy and Evelyn method. A superficial consideration of the 1 min and 15 min Malloy and Evelyn values for D I Q would suggest that these might be of considerable value in the differential diagnosis of the two forms of jaundice, but it must be remembered that few cases of retention jaundice show bilirubin contents greater than 4 mg per 100 cc and the D I Q readings at 1 min and 15 min therefore would correspond to about 0.2 and 0.5 mg per 100 cc respectively. At this level measurements of optical density by many photo-electric devices are relatively inaccurate unless inconveniently large depths of solution are used, and even then measurements may be rendered inaccurate by minor variations in clarity of the solutions. For routine work, therefore, it is preferable to measure the Malloy and Evelyn D I Q at 30 min, that is, at the same time as the total bilirubin. With this technique, the two forms of regurgitation jaundice, as typified by acute hepatitis and obstructive jaundice, give almost identical distributions of D I Q and are quite indistinguishable by such measurements. Neither the direct van den Bergh reaction nor any of its modern modifications enable one to distinguish between the jaundice of acute hepatitis and that due to obstruction. In retention jaundice the D I Q is generally, but not

HYPERTENSION AND UNILATERAL KIDNEY DISEASE¹

By G J LANGLEY AND ROBERT PLATT

(From the Department of Medicine, Manchester University)

Introduction

THE syndrome of unilateral renal disorder and hypertension is of great interest for three reasons. Firstly, it was discovered as a result of a logical argument, experimental work had shown that the syndrome might exist, clinicians sought and found it, and removal of the disordered kidney brought about the anticipated cure. Secondly, many of the cases cured by nephrectomy have been of such severity that they would otherwise rapidly have died from hypertension. Thirdly, their cure has provided the first conclusive proof that human hypertension, even of the malignant type, can be directly caused by disease of the kidney, and that the effects of hypertension, even when profound, may be reversible. It is not strictly true to say that the syndrome was discovered only after the work of Goldblatt, Lynch, Hanzal, and Summerville (1934) and Wilson and Byrom (1939), because Schwarz (1924) and Ask-Upmark (1929) had previously described cases of hypertension in which only one kidney was found at post-mortem examination to be diseased, and Quinby (1923) and Crabtree (1927) had actually recorded cases in which nephrectomy undertaken for some urological disorder was followed by cure of the accompanying hypertension. In these cases the lowering of the blood-pressure was merely incidental, and it was not until Butler published his case in 1937 that the possibility of nephrectomy for the deliberate cure of hypertension was appreciated. Since that time a large number of cases of nephrectomy for hypertension has been recorded, some successful and others unsuccessful, and several reviews of the subject have been published. Few of the authors, however, come to any conclusion as to why only some of the cases are successful, and those who lay down any criteria for selection seem to us in some instances to have chosen arbitrary standards which are not supported by the facts.

The object of the present paper is to review the recorded cases and attempt to find some guiding principles which will help others in the selection of cases for nephrectomy. We have collected from the literature 93 cases in which the data are sufficient for study, and to these we are adding 10 cases hitherto unpublished. There is no claim that the list is complete, but we believe that it summarizes the great majority of cases in the British and American literature. Continental reports have been difficult of access on account of

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regurgitation jaundice, can occur in retention jaundice complicated by liver damage

Grants from the Central Research Fund of the University of London, and from the Medical Research Council, enabled special necessary apparatus and chemicals to be purchased

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the war Before attempting an analysis of these cases, we will first consider the reviews and general articles which have been written on the subject Yuile (1944) in an interesting paper surveyed the cases in which obstruction of main renal arteries has been associated with hypertension Most of these cases were discovered at post-mortem examination and are not therefore appropriate for our purpose Hines and Lander (1941) recorded 264 patients who had attended the Mayo Clinic for various (surgical) urological disorders and were seen again 10 to 15 years later They showed that the number of cases developing hypertension was not significantly different from the number in a control series who had had no urological disorder They showed clearly, however, that patients with a raised blood-pressure at the first visit, whether in the urological or the control group, were the ones prone to develop established hypertension in later years They also noted that the incidence of familial hypertensive disease was five times as great in the patients who developed hypertension as in those who did not The authors remarked that their study did not disprove a relationship between renal disorder and hypertension in certain cases Rath and Russek (1945) also showed that urological cases as a whole are not abnormally prone to develop hypertension, but did not deny the causal relationship in individuals These two papers merely demonstrate that unilateral renal disease is not a common cause of hypertension, and this of course is generally acknowledged A striking demonstration of the relationship between hypertension and renal disorder is the case recorded by Bugbee (1943) One kidney had already been removed, and an operation was being performed on the remaining kidney for the removal of a calculus Traction on the pedicle of the kidney or pressure on the renal artery caused an immediate rise in blood-pressure from 120/80 to 230/120 The experiment was repeated several times during the operation Schroeder and Fish (1940) recorded a number of cases, many of which had clear evidence of bilateral disease and a family history of hypertension, and failed to respond to nephrectomy The cases in fact were for the most part quite unsuitable Schroeder and Fish laid down the following criteria for operation

- 1 The arterial hypertension must be of recent origin (arbitrarily placed at two years)
- 2 The renal lesion must be confined to one kidney and must have produced a diminution of function of this kidney
- 3 The combined renal function of both kidneys as determined by urine concentration and urea clearance must be within normal limits
- 4 Retinitis should be absent and the changes in the retinal vessels minimal
- 5 The arterial blood-pressure must be persistently elevated

The first and fourth of these propositions are disproved by an analysis of the published cases, as we shall show later on The fifth proposition is self-evident, if the operation is to be undertaken solely for the relief of hypertension, then hypertension should unquestionably be present That these

criteria have been tacitly accepted is shown by the fact that they are quoted and endorsed by Abeshouse (1941) in his review of the subject. Sensenbach (1944), who recorded 75 cases from the literature, concluded that the diseased kidney should be functionless or its function greatly diminished, that the opposite kidney should function normally, that the hypertension should be of short duration, and that, other factors being equal, the younger the patient the greater the chance of favourable results. We do not doubt the wisdom of these statements as generalizations, but it is noteworthy that the only successful case personally recorded by this author was the oldest of the four and had had hypertension for at least nine years. Braasch has published several statements on unilateral renal disease and hypertension, but unfortunately rarely gave details of his cases. He stated (1942) that permanent recovery after the age of 50 years is rare, which is not entirely borne out by our analysis. Even in carefully selected cases he says that only 1 in 3 patients are permanently cured of hypertension, but in atrophic pyelonephritis about 60 per cent recover and in renal tuberculosis with hypertension, 50 per cent. Calculus and hydronephrosis give the poorest results with only 25 per cent of successes. Such reviews have their value, but it would be more interesting to know why only one case in three is successful (if that is a fact) and how the successful case could have been distinguished from the others. To this question Braasch gives no answer. According to Braasch, Walters, and Hammer (1940), the following are contra-indications to operation—extensive bilateral renal disease, extensive degenerative changes in other organs, advanced renal insufficiency, and a serious unrelated but inoperable lesion elsewhere in the body. These contra-indications are for the most part self-evident, but may well be emphasized in view of the unjustified enthusiasm with which some surgeons have removed kidneys in hypertensive patients. In another paper Braasch (1941) estimated that less than one per cent of hypertensives are amenable to treatment by nephrectomy, and wisely stated that it is not necessary to submit all elderly hypertensives to a searching urological examination unless the clinical history and examination suggest the likelihood of unilateral disease. He remarked that in some cases nephrectomy may be justifiable on the chance that it may prove a cure, even though the indications are not entirely clear. He repeated that success is unlikely above the age of 50 years. Palmer, Chute, Crone, and Castleman (1940), who summarized the literature to that date, noted that 22 per cent of cases of so-called essential hypertension showed abnormalities on intravenous pyelography, and nearly three-quarters of these had a unilateral lesion. A family history of hypertension was obtained in 76 per cent of the hypertensive patients, and in only 40 per cent of cases of pyelonephritis without hypertension. The individual family histories of their nine recorded cases of nephrectomy for hypertension are, unfortunately, not described. Only one of the cases was successful. In order to save space we have not tabulated the details of the 93 cases which we have studied from the literature, neither will the authors be individually referred to in

the text. A full bibliography of the papers from which the information has been compiled is given in the References, and our own cases are briefly described in the Appendix.

Analysis of 103 cases

Results We have classified the results of nephrectomy as follows. In 47 cases the blood-pressure was restored to normal and remained normal for

TABLE I

Results in 103 Cases

Successes	47
Failures	37
Partial successes	6
Doubtful	13
	<hr/> 103

TABLE II

Effect of Age

	Average (years)	Range (years)
Successes (46 cases)	29.6	2 to 63
Successes (omitting those under 20 years) (29 cases)	40.8	27 " 63
Failures (27 cases)	37.6	20 " 60
Partial successes (6 cases)	37.3	18 " 52
Doubtful (13 cases)	35.4	7 " 62

the period in which the case was followed up, which was usually more than one year. In 37 cases there was obvious failure to reduce the blood-pressure significantly, and in some cases it was higher after the operation. In six cases there was a significant fall in pressure, though not to normal, and in 13 cases the result has been recorded as doubtful on account of inadequate data or short follow-up period. These results are recorded in Table I. It is not suggested that they are of much value in assessing the probability of cure, since there is a strong and natural tendency to record successes rather than failures. Nevertheless, this summary of results has to be made in order to assess the relative significance of the number of successes and failures in the various groups into which we have divided the cases (Tables II to VI).

Age The ages of the patients are not recorded in every case. The average ages for successes and failures are shown in Table II. Nearly all the cases under 20 years of age were successful, and a separate average has therefore been calculated after excluding these. This shows that age of itself does not contra-indicate operation. There were 16 patients over 45 years of age in whom a definite result was recorded. Of these, 11 were cured and five were unimproved by nephrectomy.

Duration of hypertension In the majority of cases the duration of the hypertension prior to operation is unknown, but there are 21 cases in which hypertension had been known to have existed for more than two years. These are recorded in Table III. It will be seen that success has been reported in patients who have had hypertension for as long as 10 years.

Significance of retinal changes In 48 cases the retinal changes are recorded. These are summarized in Table IV. The degree of retinal change appears to have little prognostic significance. In particular it may be remarked that those cases in which papilloedema was present were strikingly successful.

TABLE III

*Cases in which Hypertension Existed for more than
Two Years before Operation*

	Number of cases	Average duration (years)	Range (years)
Successes	9	4.7	2 to 10
Failures	9	6.0	2 „ 10
Doubtful	3	—	—

TABLE IV

Effect of Eye Changes

	Successes	Failures	Partial successes	Doubtful
Retina normal	10	11	3	1
Vascular changes only	3	1	—	1
Haemorrhages	1	1	—	—
'Retinitis'	3	3	—	—
Papilloedema (with or without other changes)	7	3	—	—

TABLE V

Influence of Heredity

	Successes	Failure	Partial successes	Doubtful
Family history of hypertensive disease positive	1	11	1	0
Family history negative	8	4	0	1
Average age (Family history +)	52	39	31	—
„ „ („ „ -)	40*	42	—	48

* Omitting two patients aged six and eight years

This, however, is explained by the fact that six of the seven successful cases with papilloedema were under 20 years of age.

Effect of heredity One of us (Platt, 1947) has recently emphasized the importance of heredity in essential as opposed to other types of hypertension. If this is accepted it follows that cases in which a family history of hypertension was present would be more likely to be cases of essential hypertension and therefore not amenable to cure by nephrectomy. That this is in fact the case is shown by analysis of 26 records in which the family history is mentioned. It will be seen from Table V that of the 13 cases with a family history of hypertension only one was successful, whereas there were eight successes amongst the 13 cases in which the family history was stated to be negative. That this is not purely due to a different age incidence is also shown in this Table. In the next section it will be seen that pyelonephritis is a more favourable finding than calculus or hydronephrosis. It should be noted, therefore, that pyelonephritis was the lesion found in five cases with

a positive family history and in six with a negative family history. The difference appears to be insignificant.

Analysis of pathological condition found In Table VI an attempt is made to group the cases in the series according to the pathological condition found

TABLE VI
Pathological Analysis

	Successes	Failure	Partial successes	Doubtful
Calculus and pyelonephritis	3	2	1	2
Calculus and hydronephrosis	2	2	0	0
Calculus and pyonophrosis (or infected hydronephrosis)	1	3	0	0
Hydronephrosis (uncomplicated)	3	4	2	1
Hydronephrosis (infected)	1	3	1	3
Pyelonephritis (usually atrophic)	12	6	1	1
Pyelonephritis (with hypoplasia)	5	2	0	0
Renal tuberculosis	3	0	0	2
Tumours {	Hypernephroma	2	0	1
	Adenocarcinoma	0	0	0
	Wilms tumour	0	0	1
Cysts	2	0	0	1
Hypoplasia	2	1	0	1
Fibrosis after operations	3	1	0	0
Atrophy after X-ray treatment	1	0	0	0
Aberrant arteries	2	1	0	0
Occlusion of renal artery	2	0	0	0
Renal infarct	1	0	0	0
Aneurism of renal artery	1	0	0	0
'Contracted kidney'	0	1	0	0
Nephrosclerosis	0	1	0	0
	46	27	6	13

(Data in 11 other cases not complete)

in the affected kidney. From this it will be seen that only three groups are large enough for any kind of statistical evaluation. There were 16 cases in which calculus was accompanied by pyelonephritis or hydronephrosis. Of these only six were successful. Of 18 cases of hydronephrosis without stone only four were successful. Of 27 cases of pyelonephritis, 17 were successful. These figures substantially confirm the conclusions of Braasch (1942) already quoted, and suggest that unilateral pyelonephritis is the condition in which nephrectomy is most likely to be successful. Unfortunately it is one of the most difficult conditions to diagnose with certainty. Rarer miscellaneous abnormalities such as hypoplasia, fibrosis after operations, and abnormalities of renal vessels, contribute materially to the total number of successful cases.

Analysis of failures In 27 fully recorded cases in which the blood-pressure failed to respond to nephrectomy, the operation was clearly indicated on surgical grounds (for example, large hydronephrosis, pyonophrosis, calculus) in no less than 15. Of the remaining 12 one died shortly after operation from thrombosis of the renal artery of the opposite side, three gave a clear history of pregnancy toxæmia, and showed only minor differences of function between the two kidneys, one (Case 8 in the Appendix) appeared to be

suitable as a case of unilateral atrophic pyelonephritis but was aged 60 years, six other cases of atrophic pyelonephritis showed only minor differences of function (that is, the evidence of unilateral disease was insufficient) Two of these had a positive family history suggesting hypertension One failure, in a case of fibrosis after previous operation, also had a family history of hypertension Of these 12 failures some were undoubtedly justifiable risks owing to the severity of the hypertension and the youth of the patient

Analysis of successes We have carefully scrutinized the successful cases in the light of the indications revealed by this analysis Out of 46 cases, there were obvious surgical indications for operation in seven In only six cases were both kidneys clearly functioning, three showed poor function on one side, and three showed a small deformed poorly functioning kidney The remainder, 33 cases, showed adequate evidence of unilateral disease usually with a functionless kidney One patient had a history of pregnancy kidney, but a unilateral non-functioning kidney made the indication for operation reasonably favourable In short the main differences between the successes and failures (omitting those in which there were surgical indications for nephrectomy) were firstly, the evidence on which the diagnosis of unilateral disease was made which was much stronger in the successful cases, secondly, the family history of hypertensive disease which was more frequent in the unsuccessful cases, and thirdly, the nature of the disease process, pyelonephritis and congenital abnormalities giving more favourable results than hydronephrosis or calculus

Conclusions

The purpose of the present review is to formulate the indications for nephrectomy in hypertension The first consideration is how far urological investigation should be carried out as a routine in hypertensive cases In our view an intravenous pyelogram should be made in all younger patients with hypertension (say under the age of 45 years), and in all cases if there is a history of 'bladder trouble', cystitis, frequency, dysuria, haematuria, or renal pain This should be followed by retrograde pyelography when necessary Investigation should also be carried out in all patients who give no indication at all of hypertension in the family, since one of us (Platt, 1947) has shown that there is at least a 3 to 1 chance that such cases are secondary to renal disease, which may be unilateral

If evidence of unilateral renal disease is found, in nearly a third of the cases there will be surgical indications for nephrectomy, such as the presence of a large hydronephrosis, and the decision in favour of operation will be relatively easy In the remainder a non-functioning kidney on one side with good function on the other is the most promising indication for success In all cases the total renal function should of course be within normal limits In doubtful cases atrophic pyelonephritis, if there is reasonable evidence that it is unilateral, is more likely to meet with success than calculus or hydronephrosis

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If evidence of unilateral renal disease is found, in nearly a third of the cases there will be surgical indications for nephrectomy, such as the presence of a large hydronephrosis, and the decision in favour of operation will be relatively easy. In the remainder a non-functioning kidney on one side with good function on the other is the most promising indication for success. In all cases the total renal function should of course be within normal limits. In doubtful cases atrophic pyelonephritis, if there is reasonable evidence that it is unilateral, is more likely to meet with success than calculus or hydronephrosis.

If other indications are clear, age by itself is no contra-indication to operation, neither is the knowledge that hypertension has already existed for a number of years. Nevertheless the decision in favour of operation will be more confidently made in young persons, since a larger proportion of them are suitable. Papilloedema is not a contra-indication to nephrectomy. A family history strongly indicative of hypertension in a middle-aged or elderly subject contra-indicates operation unless the evidence of unilateral disease is abundantly clear. A history of pregnancy toxæmia has the same significance. Finally, in some cases the operation may be justifiable even though the indications are doubtful on account of the youth of the patient and the severity of the hypertension, the prognosis being extremely unfavourable if no intervention is attempted. Unexpected successes have sometimes occurred in this way.

The operation of thoraco-lumbar sympathectomy for hypertension affords an opportunity of inspecting the kidneys, and in cases where unilateral renal disease is a possibility it should be performed first on the side of the suspected kidney. A nephrectomy can then be carried out if the indications appear to be favourable, for instance if atrophic changes, renal deformity, perirenal fibrosis, or abnormal renal arteries are found. In most of the failures the evidence that the renal disease was unilateral has been unconvincing.

Our thanks are due to colleagues who have kindly allowed us to consult the records of Cases 9, 10, and 11.

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APPENDIX

Case 1 (Previously reported by Platt (1942)) Female, aged 8 years First seen 22 5 41

History Severe headache and vomiting six months One year ago recurrent pyrexia *B coli* infection of urinary tract found Intravenous pyelograms showed functionless left kidney No note of blood-pressure at that time Father, mother, and siblings well No family history of hypertension

Examination Pale child Blood-pressure 200/120 Bilateral papilloedema (two dioptries), retinal oedema, macular exudates Urine 1010 Trace albumin No pus or casts Blood, non-protein nitrogen, 52 mg per 100 c c (? accuracy—specimen inadequate, veins poor)

Progress May 29 blood-pressure 220/120 May 30 cystoscopy, dye excreted by right kidney in five minutes, left kidney nil Left nephrectomy Small hypoplastic kidney, $1\frac{1}{2}$ inches in length End of operation, blood-pressure 190/120 Four hours later, 160/128 Next day, 145/? 30 7 41 blood-pressure 140/90 No further symptoms Appearance much improved Retina improving 15 10 41 blood-pressure 125/70 No papilloedema Exudates clearing April 1942 blood-pressure 115/75 Well Exudates just visible May 1946 (five years after operation) A normal healthy child of 13 years, blood-pressure 115/80 Blood-urea 32 mg per 100 c c Urea clearance 77 per cent

Pathology Four small renal arteries No sign of main arterial trunk. Congenital hypoplasia Glomerular fibrosis Endarteritis Chronic pyelonephritis

Result Successful

Case 2 Male, aged 48 years First seen 31 12 42

History Four years ago unsuccessful operation for calculus (left) Two years ago a further attempt, stone still not found Two months ago attack of aphasia

Examination Blood-pressure 270/170 (later 180/100) Blood-urea 32 mg per 100 c c Urea clearance 97 per cent Fundus nil Intravenous pyelograms, slightly enlarged right kidney, deformity of calyces left and calculus in pelvis Urine contains pus Cystoscopy indigo-carmin right five min, left nil Operation (Mr Macalpine) 2 2 43 Much surrounding fibrosis Left nephrectomy Kidney normal in size Capsule adherent Surface finely granular

Progress 4 2 43 blood-pressure 150/100 6 5 43 blood-pressure 130/90 Feels well Throbbing headache and dyspnoea has gone 8 5 45 slight hemiplegia 10 days ago Blood-pressure $\frac{250-240}{160}$ (pulsus alternans) June 1945 died

Pathology Chronic atrophic pyelonephritis

Result Failure (Temporary improvement)

Case 3 Female, aged 31 years First seen 16 6 42

History Swelling of ankles 12 months Palpitation and dyspnoea 18 months Father died of cerebral thrombosis after high blood-pressure Mother ill with dropsy

Examination Blood-pressure 210/130. No oedema No retinopathy Blood-urea 46 mg per 100 c c Urea clearance 102 per cent No pyuria

Intravenous pyelograms Left kidney enlarged, no shadow right Cystoscopy, indigo-carmine, nil right or left (10 min) Catheter could not be passed into right ureter (obstruction $\frac{1}{4}$ inch above bladder)

Progress 12 9 42 blood-pressure 185/135 14 9 42 large right hydronephrosis removed containing nine pints of straw-coloured fluid 24 9 42 blood-pressure 135/100 27 9 42 blood-pressure 130/100 10 11 42 blood-pressure 160/110 April 1943 blood-pressure 165/110 October 1946 could not be traced

Pathology Hydronephrosis with hyaline arteriosclerosis Compatible with benign hypertension

Result Partial success (Family history of hypertension) Operation justified on surgical grounds

Case 4 Male, aged 48 years First seen 6 10 43

History Six months headache and dyspnoea

Examination Pallor Heart enlarged Blood-pressure 260/180 No oedema Retinitis and papilloedema Urine nil Blood-urea 42 mg per 100 c.c Urea clearance 77 per cent Intravenous pyelograms, calculus right kidney, poor excretion left

Progress 9 11 43 large right hydronephrosis removed 11 12 43 blood-pressure 180/130 February 1944 blood-pressure 270/180 June 1944 blood-pressure 250/180 November 1944 blood-pressure 230/180 8 1 45 died

Pathology Hydronephrosis

Result Failure (possibly bilateral disease)

Case 5. Male, aged 41 years First seen 28 4 43

History 1926 right renal colic 1929 passed stone 1930 passed another stone 1936 renal colic No stone found Right renal sympathectomy (Blood-pressure not recorded) Present symptoms, anginal pain on exertion Father died arteriosclerosis at 70 Mother well at 85 Brother has high blood-pressure

Examination Blood-urea 35 mg per 100 c.c Urea clearance 117 per cent Intravenous pyelograms Right renal pelvis dilated, left normal, both function Cystoscopy, indigo-carmine right 7 min, left 6½ min

Progress 8 6 43 blood-pressure 210/140 Right nephrectomy 26 11 43 blood-pressure 180/120 22 10 46 dyspnoea, headache Blood-pressure 225/155 No papilloedema

Pathology Essential hypertension

Result Failure (Evidence of unilateral nature of the disorder inadequate)

Case 6 Male, aged 42 years First seen 22 2 44

History Left lumbar pain and haematuria 1 month Cardiac pain 3 months ago Headaches 3 years Father died cerebral haemorrhage at 78 Mother died cerebral haemorrhage at 56 Mother's sister died cerebral haemorrhage at 49 Maternal grandmother died cerebral haemorrhage at 56 Paternal grandmother died suddenly (heart) at 63

Examination Blood-pressure 220/120 Urine clear No retinopathy Intravenous pyelograms Left excretes No hydronephrosis seen Right excretes subnormally Cystoscopy, indigo-carmine right 6 min, left nil Retrograde pyelogram, hydronephrosis left

Progress 25 2 44 left nephrectomy 19 3 44 blood-pressure 180/120.

APPENDIX

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Pathology Four small renal arteries No sign of main arterial trunk Congenital hypoplasia Glomerular fibrosis Endarteritis Chronic pyelonephritis

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History Four years ago unsuccessful operation for calculus (left) Two years ago a further attempt, stone still not found Two months ago attack of aphasia

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Pathology Chronic atrophic pyelonephritis

Result Failure (Temporary improvement)

Case 3 Female, aged 31 years First seen 16 6 42

History Swelling of ankles 12 months Palpitation and dyspnoea 18 months Father died of cerebral thrombosis after high blood-pressure Mother ill with dropsy

Examination Blood-pressure 210/130 No oedema No retinopathy Blood-urea 46 mg per 100 c c Urea clearance 102 per cent No pyuria

show dilatation The pathologist comments 'It is reasonable to infer that the contra-lateral kidney will contain similar arteriosclerotic lesions and that hypertension will persist'

Result Failure

Case 10 Female, aged 20 years

History Admitted April 1943 Headaches several years Father 44, mother 43, sister 16, all well

Examination Blood-pressure 210/120 Urine negative No papilloedema Blood-urea 26 mg per 100 c c Urea clearance 55 per cent Intravenous pyelograms, both kidneys functioning well, right upper calyx appears enlarged Retrograde pyelogram suggests developmental abnormality in right kidney

Progress 7 7 43 blood-pressure 180/110 8 7 43 right nephrectomy 19 7 43 blood-pressure 140/100 Discharged 13 8 43 Blood-pressure 150/105 No headache since operation 15 9 43 blood-pressure 185/120 Blood-urea 36 mg per 100 c c Urea clearance 40 per cent

Pathology Kidney normal in size Pelvis shows congestion Surface shows fibrous depressed areas Right upper calyx dilated Section shows healed chronic pyelonephritis with hyaline changes in arterioles

Result Failure Evidence of unilateral disease inconclusive Urea clearance suggests bilateral disease, but operation justified owing to age of patient

Case 11 Female, aged 55 years

History Admitted 30 3 38 Weakness and numbness of hands, feet, and legs Occasional double vision

Examination A series of blood-counts showed leucocytosis with 35 to 60 per cent of eosinophils Urine, albumin present Sterile Blood-urea 20 mg per 100 c c Urea clearance 63 per cent Cerebrospinal fluid normal Weakness and muscular wasting in the hands All reflexes present Blood-pressure not recorded December 1943 admitted to a hospital in London Eosinophilia continues, probably periarteritis nodosa Readmitted 27 1 45 Headaches, temporary aphasia, pains in limbs

Family history Father died of cancer Mother died of stroke Ages not recorded

Examination Blood-pressure 230/140 No papilloedema, no exudates Heart enlarged Reflexes all present No sensory loss Blood-urea 28 mg per 100 c c Urea clearance 48 per cent Intravenous pyelograms show non-functioning right kidney with calculus in ureter

Progress 19 7 45 blood-pressure 240/130 20 7 45 right nephrectomy 31 7 45 blood-pressure 215/115 7 8 45 blood-pressure 190/100

Pathology Hydronephrosis, with extensive fibrosis and atrophy

Result Failure Probable periarteritis nodosa in addition to hydronephrosis The low urea clearance suggests that both kidneys were affected

7 4 44 blood-pressure 170/135 22 12 44 blood-pressure 200/130 28 5 46 blood-pressure 195/130

Pathology Slight hydronephrosis Essential hypertension

Result Failure (Evidence of unilateral nature of the disorder inadequate Strong family history)

Case 7 Female, aged 40 years First seen 11 1 44

History Chest trouble 5 years Headache 3 years Father well at 66 Mother died seizure at 56 Three sisters well

Examination Obesity Heart enlarged Blood-pressure 280/160 Early papilloedema Blood-urea 29 mg per 100 c c Urea clearance 73 per cent Urine nil Intravenous pyelograms, non-functioning right kidney Retrograde pyelogram, right hydronephrosis

Progress 21 4 44 blood-pressure 270/190 Right nephrectomy 1 5 44 blood-pressure 205/115 9 6 44 blood-pressure 255/155 1946 not traced

Pathology Hydronephrosis (Sections not traced)

Result Failure Operation justified on the evidence of hypertension with functionless kidney

Case 8 Female, aged 60 years First seen 13 6 46

History Seven years ago severe headache, hypertension discovered Improved for four years One year and nine months ago, headache increasing, vision poor (cataract in right eye) No previous history of kidney disease, frequency, or dysuria Three normal pregnancies Father died young, mother died at 70, cause unknown

Examination Blood-pressure 250/136 Heart slightly enlarged Blood-urea 38 mg per 100 c c Urea clearance 79 per cent Urine contains pus cells and *B coli* Became sterile after treatment Intravenous pyelograms Left kidney normal (rather large), right kidney functionless

Progress Blood-pressure became 180/110 12 8 46 right nephrectomy Small atrophic kidney removed Uneventful recovery, but on 19 9 46 blood-pressure 220/130

Pathology Small kidney 6 x 3.5 cm Surface finely granular, capsule adherent, pelvis dilated Microscopically, all glomeruli have disappeared Tubules are dilated, filled with pink-staining casts Large arteries show obliterative intimal sclerosis Diagnosis, healed chronic atrophic pyelonephritis

Result Failure This may have been a primarily hypoplastic kidney

Case 9 Female, aged 44 years

History 19 3 44 diplopia, with ptosis of the left eyelid No other complaint, but there was a previous history of rheumatism seven years before, and of urinary frequency since the birth of her first child 15 years ago Four pregnancies, no pregnancy toxæmia Father died of a stroke (age not stated) Mother died of 'gallbladder trouble'

Examination Blood-pressure 260/140 No retinitis Urine contains pus cells and staphylococci Blood-urea 25 mg per 100 c c Urea clearance 89 per cent Intravenous pyelograms, left kidney normal, right not outlined Retrograde pyelogram, dilated pelvis, and major calices right

Progress 22 6 44 right nephrectomy 7 7 44 discharged Blood-pressure still 230/120

Pathology Kidney, of normal size, shows chronic pyelonephritis with extensive hyaline arteriolar sclerosis A few glomeruli are sclerotic, tubules

THE AETIOLOGY, DIAGNOSIS, AND TREATMENT OF PROLAPSED INTERVERTEBRAL DISK, WITH A REVIEW OF 300 CASES OF SCIATICA¹

By DAVID KENDALL

THE term *sciatica* was used up to the middle of the eighteenth century to indicate any painful condition in the region of the hip, and it was not until 1764, when Cotugno published his treatise on the nervous *sciatica*, that any attempt was made to narrow the concept of *sciatica* to its present-day standard. This writer recognized two varieties of sciatic pain, that in which pain is confined mainly to the region of the hip, associated with an arthritis of the hip joint, and that in which pain occurred in the course of the sciatic nerve. The latter variety was ascribed to an inflammatory condition of the nerve, the pathological basis of which, though a delight to the reader in its ingenuity, is a masterpiece of wishful thinking. It is, however, worthy of note that many more recent ideas of the causation of *sciatica* have been based upon grounds almost as dubious, and it is perhaps true to say that in this malady it has too often been a case of theory being the father to the facts. Since the time of Cotugno's writing a great deal has been written on the subject, and for many years *sciatica* was regarded as a form of neuritis (Gowers and Taylor, 1899) and it was not until 1903 that some doubt was cast upon the neuritic theory by Bruce who found little evidence to support the theory of active inflammation of the sciatic nerve. He found that tenderness was not a prominent feature of the disease and, on the assumption that trauma played a part in the production of the supposed neuritis, pointed out that the sciatic nerve is much less subject to trauma than, for example, the ulnar nerve. Why, therefore, is not 'ulnitis' commonly met with?

In recent years the neuritic theory has lost ground, but Harris (1938) adhered to the concept of an inflammatory process in the sciatic nerve sheath. The position with regard to *sciatica* at about that time was aptly described by Wilson (1940) who stated 'owing to its multiple causation a unique pathology for *sciatica* can hardly be expected, at the same time the problem of how the pain arises is not solved by the morbid conditions described'. Much has been made at various times of the part played by the sacro-iliac joints in the production of sciatic pain (Goldthwait and Osgood, 1905, Verrall, 1924, Smith-Petersen and Rogers, 1926, Yeoman, 1928), but it is very doubtful whether disturbances of these joints can account for more than a fraction of cases of *sciatica*. Adams (1923) suggested that abnormalities of the fifth lumbar vertebra might be an aetiological factor, a suggestion that appears to have been finally disproved by Brailsford (1928),

¹ Received December 10, 1946

The average age for the whole series is 34.9 years, a figure somewhat below that usually stated to be the mean of any relatively large series of cases of sciatica. Of the earlier writers, Gibson (1893) in an analysis of 1,000 cases found the average age to be over 40 years. Yeoman (1928) found an average age of 44 years in a series of 100 cases.

Age	Gibson	Present series*
10 to 14	0	2
15 " 20	14	13
21 " 30	159	81
31 " 40	310	120
41 " 50	248	41
51 " 60	187	15
61 " 70	71	1
71 " 80	11	0

* Excluding Groups C and D, on account of the diversity of aetiological factors in these groups

The sex incidence in the present series is, generally speaking, in accord with that of most previous writers. All are agreed that sciatica affects male patients predominantly.

The Aetiology of Sciatic Pain

In the present series only two aetiological factors appeared to play a prominent part in the production of sciatic pain—trauma and exposure to cold or damp. This is no new observation, having been made by Cotugno and almost every writer since his time. These factors were found to have been present in varying degree in sciatica both due to disk protrusion and myofascial causes. In the latter, a third factor, the so-called 'rheumatic' predisposition also plays a part. The table below shows that exposure to cold and 'rheumatic' symptoms play only a small part in the aetiology of disk protrusion, whereas the reverse is true of myofascial sciatica.

	Trauma		Exposure	Trauma and exposure	'Rheumatic' symptoms	Removal of disk
	Severe	Mild				
Prolapsed disk	27	106	0	6	0	22
Myofascial sciatica	0	40	33	7	25	5

In considering the clinical histories two types of trauma are evident, a single relatively severe injury and repeated minor injuries. The more severe injuries are very constant in their character in cases diagnosed as prolapsed disk, the history being almost always of a fall from varying heights onto the feet or buttocks with the spine in an attitude of flexion. In these cases symptoms usually date from the time of injury whereas in the repeated minor traumata more variation is found. The history in the latter type is often one of the lifting of heavy weights, and in particular the lifting of weights in circumstances of mechanical disadvantage, for example, unloading a lorry from ground level. Turning the engine of a heavy motor vehicle is frequently the precipitating factor of an attack of sciatic pain. Two cases (both of which were confirmed at operation) followed lumbar puncture,

who found developmental abnormalities in 26 per cent of 3,000 X-rays of the lumbosacral region. More recently, Bankart (1942) has stated that 'spinal arthritis is the commonest cause of sciatica'. Hurst (1943) implied that a large proportion of cases of sciatica are either primarily or secondarily of the nature of a psychoneurotic disorder. Clearly if so many hypotheses can co-exist upon the nature of sciatica, and in addition so many methods of treatment be employed in a disease which is admittedly often self-limiting, these hypotheses must be based upon lack of exact knowledge of the underlying pathological process or faulty interpretation of physical signs.

The patients in the present series were investigated during the course of three years at a neurosurgical centre, at two emergency hospitals each with a large orthopaedic unit, and at St Thomas's Hospital. A large proportion (approximately 60 per cent) consisted of patients in the Services, so the average age is somewhat lower than is generally recorded in other investigations made in times of peace. The cases fall into three main diagnostic groups:

- A Intervertebral disk protrusions
- B Inflammation or disease of muscular or fascial structures
- C Cases in which there was involvement of the cauda equina, sacral plexus, or sciatic nerve by gross disease of neighbouring structures
- D Cases having a functional basis

The age and sex incidence in the series are set out in the following tables. Groups C and D are not included except to show the number of cases in the groups, the primary diagnosis being arranged in a separate list.

Group A	Group B	Group C	Group D
Prolapsed inter-vertebral disk	Disease of myofascial structures	Miscellaneous causes	Psychological origin
*163 (53 %)	110 (36 %)	20 (7 %)	12 (4 %)
Total—305 cases			

* This figure represents the total number of cases in which a diagnosis of prolapsed intervertebral disk was made either clinically or clinically and radiologically. It does not represent the number of confirmed diagnoses, as only 118 of these cases were submitted to laminectomy.

	Male	Female	Average age
Group A	134 (82 %)	29 (18 %)	32.7 years
Group B	94 (85.5 %)	16 (14.5 %)	32.9 „

(There was a slight predominance of males in the population from which the cases were drawn.)

Group C	
Primary diagnosis	Number of cases
Spondylolisthesis	3
Spondylitis ankylopoietica	2
Osteoarthritis of hip	7
Gonococcal arthritis	2
Tumour of cauda equina	1
Sarcoma of pelvis	1
Carcinoma of rectum	1
Metastasis from lung carcinoma	2
Herpes zoster	1
Group D	
Psychoneurosis	12
Total—32 cases	

recovery usually occurs in two to three weeks. The duration of symptoms appears to be largely independent of treatment, heat, massage, and analgesics do no more than give symptomatic relief. The less severe cases may be ambulant, a fact which does not seem to bring about any prolongation of the period of symptoms. There is a marked tendency for attacks of back pain due to disk prolapse to recur. The second and subsequent attacks sometimes follow trivial trauma or exposure, or occur spontaneously. Attacks of this kind may be repeated over a period of several years before the appearance of any additional symptoms and signs. Pain of this type occurred in 98, or 61 per cent of the 163 cases falling into this group, and was of a remittent character in 80 per cent. The majority of patients here considered did not come under observation until further symptoms had occurred in addition to back pain, the average total length of history being in the neighbourhood of two years, the longest was 19 years and the shortest three months.

Duration of Symptoms on Admission to Hospital

Less than 1 year	28.8%
1 to 3 years	42.5 "
3 " 5 "	16.2 "
Over 5 years	12.5 "

Pain in the lower limb may follow upon back pain after a varying interval, and in some 40 per cent of the cases was the initial symptom. The distribution and character of this pain is variable. Most commonly it is felt in the buttock, the back of the thigh, and on the outer side of the leg and foot. Frequently there is an apparent gap from the knee to the ankle in which pain is not felt. It is of interest to note that a considerable number of patients spontaneously offered the information that the leg and foot pain differed from that felt in the buttock and thigh. The latter is usually described as a dull gnawing or aching sensation apparently deep in the substance of the limb, whereas the pain in the leg and foot is varyingly described as a sharp stab, a painful numb feeling, or a burning sensation, and tends to be more intermittent and more subject to alteration by movement and exertion than that in the thigh. The pain in the foot has in fact many of the characteristics of true root-pain. Many of the patients who did not volunteer this information stated on direct questioning that there was a distinction in the pain between the two situations mentioned. Pain in the leg may or may not be associated with pain in the back. It tends to be aggravated by movement, particularly by spinal flexion or any exertion, and often makes sitting for any length of time extremely uncomfortable. The effect of posture varies. On the whole, those who are not in very severe pain are more comfortable standing than lying down. Rest gives some relief, but sleep is often disturbed by sudden exacerbations. Paraesthesiae in the form of a sensation of pins and needles in the leg or foot occur in a small number of patients and do not necessarily coincide with the presence of any

which procedure had, it appeared, been performed with much difficulty and was accompanied by considerable pain in the back. Congenital abnormalities of the lumbar spine, excluding spondylolisthesis, were found in approximately 12 per cent of cases. A similar figure was obtained in the radiographic examination of the lumbar spines of some 50 patients suffering from conditions other than sciatica. It is not therefore considered that such defects as sacralization of the fifth lumbar vertebra, spina bifida, and articulation of the fifth lumbar vertebra with the sacrum or ilium have any direct bearing on the production of sciatic pain. Exposure to cold and damp does not play a prominent part in the production of the initial symptoms of a prolapsed disk, but a recurrence of these symptoms is not infrequently precipitated in this way. Exposure includes sleeping in the open, working in damp clothes, and subjection to frequent variations in external temperature, all of which factors are inevitably prominent in considering a series of cases which includes a large number of Service personnel.

The Symptoms of Disk Protrusion

The symptoms of the typical case of prolapsed intervertebral disk consists of three main phases—the initial trauma, the onset of pain in the back, and the onset of pain in the leg. The relationship of the onset of symptoms to trauma is variable. Back pain may follow immediately upon the injury or accident or there may be a brief interval, or the two events may be only remotely associated in time. The findings in the present series are set out below. Eighty-six per cent of cases had suffered trauma of varying degree

Immediate onset	Delayed up to six months	Remote
72 %	24 %	4 %

Thus it will be seen that the onset of symptoms is most commonly associated with very recent trauma. The initial pain is fairly constantly referred to the lumbar region and is most commonly felt in the midline, with a tendency to spread laterally on both sides. At times the pain radiates into one or both buttocks and occasionally into the posterior aspect of the thigh on one or other side. It is rare for the pain to extend into the calf or the foot at this time. The pain varies greatly in severity, both in the same case and from one case to another. It may be relatively trivial, or may have all the character of the condition usually regarded as lumbago. In the latter instance the pain is intense, movement is resented, the spine is held rigidly, usually slightly flexed, and there is obvious spasm of the paraspinal muscles. Whether the pain is slight or severe it is characteristic that the patient is unable to find any posture which gives complete relief. Sleep is apt to be disturbed by sudden exacerbations of pain. Usually movement of the spine is both painful and restricted, particularly flexion, which may be impossible owing to the degree of muscle spasm present. As is to be expected in any condition in which muscle spasm plays a part, coughing and sneezing aggravate the pain. This phase of the syndrome is self-limiting, and slow

suggested by the fact that the scoliosis may at different times change its direction in any one patient, and that there is no constant relationship between the site of the disk protrusion and the related nerve root on the one hand, and the direction of the scoliosis on the other. The writer has gained the impression that a scoliosis is less common when the disk protrusion lies between the fifth lumbar vertebra and the sacrum than when between the fourth and fifth lumbar vertebrae. The scoliosis is usually accentuated on flexion or attempted flexion of the spine with the legs straight. It is significant to note that during flexion there is a tendency for the affected heel to be lifted off the ground by an increase in the pelvic tilt together with flexion at the knee. Some patients, on resuming the upright posture after flexion, display a curious lurch of the trunk upon the pelvis which gives the impression of a momentary undoing of the scoliosis. The scoliosis and flattening of the lumbar spine usually persist in some degree during a period of spontaneous remission of symptoms. Some disturbance of spinal movement, both passive and active, is invariably present. Characteristically flexion is grossly restricted. Extension also is usually very limited. In a severe case virtually no flexion or extension of the lumbar spine can be detected clinically. In marked contrast to this is the presence of full lateral flexion to each side, together with a normal range of rotatory movement.

The neurological signs may be classified as follows—local tenderness, Lasègue's sign, and motor, sensory, and reflex disturbances. Local tenderness was present in approximately half the cases under review, its situation was variable, but in general was confined to the region between the lumbar spine and the popliteal space. In no case could any tenderness be elicited below the knee, except in four patients who displayed cutaneous hyperaesthesia on the foot. As a rule the tenderness is difficult to localize, is to be found on deep palpation of the posterior aspect of the thigh, and is less marked in the midline of the thigh than laterally and medially. The tenderness in the thigh is not confined to the course of the sciatic nerve, but is such as would be expected on palpation of muscles in spasm. Less commonly a similar diffuse tenderness is found in the buttock or lumbar region, the tenderness in the latter area being usually in the erector spinae muscles of the affected side. Lasègue's sign was the most constant of all the findings and was positive in every case. The test as originally described consisted of flexing the hip on the affected side with the patient recumbent, and subsequently extending the knee until pain is felt. The method here adopted differs in that the leg is raised with the knee extended from the first until the patient resists on account of pain. The majority of patients were unable to tolerate raising of the leg in this manner to more than 45°, some could scarcely bear the leg to be lifted from the bed. The pain thus induced is most often referred to the upper gluteal and lumbar regions of the same side, less frequently it causes an exacerbation of the pre-existing pain and radiates to the ankle and foot. Very intense pain results if the elevated limb is suddenly allowed to fall to the bed, and is usually felt in the lumbar

objective disturbance of sensation These paraesthesiae when present are usually initiated or aggravated by coughing, sneezing, or flexion of the spine The pain in the leg may, like the pain in the back, be subject to remission, either spontaneously or as a result of rest At times it may disappear with quite dramatic suddenness in a period of 24 hours or less To summarize, the typical history in patients with prolapsed intervertebral disk, is one of trauma, followed by intermittent pain in the back, in turn followed by pain in the leg also liable to remission, and often consisting of two distinct types.

The physical signs associated with this condition fall into two main categories, those which are primarily mechanical, and those indicative of disturbed nervous function The general aspect of the patient does not present any characteristic features The ambulant patient may display a limp, usually with a lurch to the affected side The gait may be shuffling, with small steps, and may give an impression of rigidity such as might be expected from one who finds walking painful The more severely affected patients are usually already confined to bed when first seen They are obviously in considerable pain and display a restlessness consequent upon their inability to find a position of comfort Each patient usually finds for himself a position of maximum comfort, often consisting of lying half on the unaffected side, with the affected leg flexed at the hip and knee Of the mechanical signs those found on examination of the back are the most outstanding An alteration in the normal curve of the lumbar spine is common, and was observed in 140 of the 163 cases in this group (86 per cent) It consists of an obliteration of the normal anterior convexity, which gives an impression of flatness to the lumbar spine, amounting at times to an actual lumbar kyphosis, of which the greatest prominence is in the region of the third and fourth lumbar spines This deformity is associated with an increase of the lumbosacral angle, that is a tendency for the lower part of the sacrum to be projected anteriorly, which in turn is secondary to a forward tilt of the whole pelvis Some degree of spasm of the erector spinae muscles is almost always present and can be both seen and palpated Usually symmetrical, it may be more marked upon the affected side Scoliosis is common, and was observed in the majority of cases in this group The direction of the deformity is variable, the concavity may be to the affected or to the unaffected side

Scoliosis

Concave to the affected side	Concave to the unaffected side	None
41 (25 %)	99 (61 %)	23 (14 %)

The primary deformity causing the scoliosis seems to be a lateral tilt of the pelvis, the affected side being elevated, it is sometimes associated with inability or unwillingness on the part of the patient to put the heel of the painful side upon the ground, a feature first observed by Lasègue (1864) Whether or not the scoliosis is to be regarded as a simple correction of the pelvic tilt is doubtful That this may be the correct interpretation is

corresponded with its whole distribution. The ankle reflex was diminished in 35 per cent of cases, lost in 28 per cent, and was normal in 37 per cent. Diminution of the knee reflex was found in 25 per cent of patients. It is of interest that the motor, sensory, and reflex disturbances, once present, tend to persist during remission of symptoms, and indeed may persist after laminectomy.

Certain accessory methods of diagnosis were used in a proportion of cases. Lumbar puncture was performed in 121 instances, but subarachnoid block was never demonstrated. Chemical examination of the cerebrospinal fluid did not show any consistent abnormality, the total protein content being raised in only 9.5 per cent of fluids examined. This finding is at variance with the experience of certain previous writers whose results are tabulated below.

Author	Number of cases	Total protein over 40 mg per 100 c c
Mixter and Barr (1934)	7	7 (100 %)
Love (1938)	265	93 (34 %)
Macey (1940)	96	60 (62.5 %)
Walsh (1939)	265	174 (66 %)

More recent writers (O'Connell, 1942, Pennybacker, 1941) have stated that the cerebrospinal fluid is usually normal, and regarded lumbar puncture as a valueless procedure in this condition. The same conclusion was arrived at in the present series, and in the more recent cases lumbar puncture was dispensed with. Radiographic examination of the lumbar spine, without the use of contrast media, is of little value in the diagnosis of prolapsed intervertebral disk, other than for the purpose of excluding gross bone or joint disease. Attempts at radiological comparison of the relative sizes of the intervertebral spaces have not met with success, nor in fact would any marked difference in these spaces be logically expected. It is only a portion of the intervertebral disk that is extruded, and there is no outward displacement of the greater part of the annulus fibrosus. Very occasionally, however, there is a definite narrowing of the intervertebral space at the site of a disk protrusion. X-rays with the use of a contrast medium (either air, iodized oil, or Pantopaque) are of some diagnostic value, although not nearly so frequently used now in this country as formerly. Contrast myelography was used extensively in earlier cases in the present series, but latterly has been dispensed with. It was considered that the degree of error was too high and the risk of aggravating the pain or causing a localized meningitis was too great to continue the use of this procedure. Further, it was considered that the history and physical signs of prolapsed intervertebral disk are sufficiently definite to justify a diagnosis without it.

The Mechanism of the Symptoms and Signs of Disk Protrusion

Reference has already been made to the very common association of trauma with disk protrusion, in particular trauma with the spine in flexion. When the spine is flexed the posterior part of the intervertebral space tends

region of the same side. In about half of the cases Lasègue's sign was positive on both sides, but it was found that the sound limb could always be raised somewhat higher than the affected one. In 20 per cent of the cases elevation of the sound limb induced pain referred to the affected side. The head and knee test was positive in 70 per cent of cases. During periods of remission of symptoms both the signs mentioned above tend to diminish in degree, although it is unusual for them completely to disappear if once they have been present. The finding of an actual diminution in voluntary power in certain muscles in the leg in association with prolapsed disk has been recorded by various writers, including Walsh (1939), 22 per cent of 285 cases, Love and Walsh (1940), 25 per cent of 500 cases, and Spurling and Bradford (1939). In the present series no motor weakness could be demonstrated other than that amount of unwillingness to exert maximum effort naturally associated with a painful condition of a limb. In 78 per cent of the present series a well-marked hypotonia of the calf muscles, usually associated with an appreciable degree of wasting, was observed. This disturbance was always confined to the affected limb. The disturbance of sensation found was variable in its distribution and severity, and sensation was never completely lost over any area, a relative hypoaesthesia to pin-prick over part of the cutaneous area supplied either by the fifth lumbar or the first sacral nerve root was the usual finding. The majority of patients subjected to laminectomy were those in whom a disturbance of sensation had been demonstrated.

Prolapsed disk	Cases	Sensory disturbance	L5	S1
With laminectomy	118	86 (73%)	21 (24%)	65 (76%)
Without laminectomy	45	12 (25%)	2 (16.5%)	10 (83.5%)

It was found that there was no constant relationship between the area of sensory disturbance and the site of the disk protrusion, as is evident from the figures concerning the site of the protrusions.

Laminectomies	Site of protrusion		None
	L4—5	L5—S1	
118	64 (54%)	28 (24%)	26

One constant feature emerged—a protrusion between the fifth lumbar vertebra and the sacrum was never associated with a sensory disturbance in the fifth lumbar distribution. The disturbances consisted of a dullness to perception of pin-prick in all but four cases in which an area of hyperaesthesia was found over the outer aspect of the foot. In general while the medial and lateral boundaries of the sensory abnormality were usually well defined on the dorsum of the foot, the upper limit was often ill defined and sometimes impossible to determine with accuracy. It was always difficult to determine the limits on the sole of the foot owing to the varying thickness of the skin. Further, in the majority of cases, the hypoaesthesia was confined to the more distal part of the dermatome involved and seldom

sensory disturbance lies in the distribution of one of the lower lumbar or upper sacral dermatomes, and is thus compatible with interference with an intraspinal nerve root by a disk protrusion in the lower part of the spinal column. In this connexion it is of interest to note the anatomical relationship of the nerve root to the protrusion. When the latter is medially situated the nerve root is found either on its lateral side or resting on its summit. When the protrusion is laterally placed the root usually lies to its medial side. Owing to the restricted field of view at operation it is not easy to determine which is the affected root, but in 19 of my cases the affected posterior root was divided intradurally. After this there was usually a transitory disturbance of sensation in the cutaneous area supplied, and it appeared that protrusions between the fourth and fifth lumbar vertebrae, although more often involving the fifth root, did sometimes involve the first sacral nerve root, particularly if the disk was medially situated.

Spontaneous remission of symptoms is not easy to account for. Cessation of pain in the back is probably a result of the subsidence of an inflammatory reaction in the damaged ligaments and a consequent relief of muscle spasm, but it is not clear why the pain due to root compression should cease, sometimes quite suddenly. It is unlikely on mechanical grounds that a disk protrusion, particularly of the sequestered type, could return to its original position, although it is probable that a postural factor brings about an alteration in the relationship of the nerve root to the protrusion. That the protrusion may make a 'bed' for itself in the vertebral body is suggested by the occasional presence of a crater-like appearance in the postero-inferior aspect of the vertebral body in lateral X-ray photographs. Other explanations of remission have been put forward by Deucher and Love (1939) who suggested the occurrence of intermittent oedema of the disk protrusion. Love and Walsh (1940) referred to a suggestion by Adson that remission is associated with an intermittent degeneration of pain conducting fibres in the posterior nerve root. Neither of these hypotheses gain support from histological examination of material removed at operation.

The majority of the physical signs present in patients suffering from disk protrusion can be explained by the mechanical condition present, for limitation of spinal flexion which is so constantly present is to be expected in view of the increased stretch imposed on damaged ligaments. At the same time the spinal canal is elongated and the dura stretched, which in turn increases the tension upon a nerve root already displaced by the disk. Limitation of extension cannot be explained in the same way, and can be accounted for only by supposing the existence of local muscle spasm, in particular in the psoas and quadratus lumborum muscles. The deformity of the lumbar spine is a defect of posture caused by muscle spasm, and is unassociated with any bony abnormality. The flattening of the lumbar spine can be accounted for in part by a forward tilt of the sacrum and pelvis, a movement which would tend to lessen the tension upon the lower lumbar and sacral nerve roots (O'Connell, 1942). Capener (1944) suggested that this deformity is a result

to increase and there is associated increase in tension upon all the ligaments whose attachments lie behind the axis of movement. Thus, in flexion the posterior common ligament, ligamenta flava, and supraspinous and interspinous ligaments are stretched. It is to be expected, therefore, that any sudden force acting directly or indirectly upon the spine in these circumstances may cause damage to any or all of these normally stretched structures, and it is probable that the initial symptoms of intervertebral disk prolapse are those of local damage to such structures in the lumbar spine. From this it follows that in this initial stage when symptoms are confined to the back, there are no signs particularly characteristic of a disk protrusion, indeed it is unlikely that actual protrusion occurs at this stage.

Roofe (1940) has demonstrated a nerve supply, not only to the ligamentous structures of the back, but also to the annulus fibrosus of the intervertebral disk. The latter is supplied through a recurrent branch which arises just distal to the posterior root ganglion and is distributed to the annulus two segments below. Inman and Saunders (1942) emphasized the sclerotomal distribution of pain in association with damage to ligamentous structures in the spinal column. Thus if damage has occurred to the ligaments in the neighbourhood of the fourth and fifth lumbar vertebrae, pain will be felt locally and will also be referred to the deeper structures of the buttock and thigh which have the same sclerotomal innervation. In addition pain may be referred by the recurrent nerves to a higher level in the back. It is suggested here that pain in the back, buttock, and posterior aspect of the thigh after injury to the lumbar spine is a manifestation of damage to ligamentous structures with associated muscle spasm, and does not depend on spinal root compression or of necessity imply the presence of a disk prolapse.

The posterior common ligament is firmly attached both to the vertebral bodies and the annulus fibrosus of each intervertebral disk, and must play a considerable part in maintaining the latter structure in position. Any injury to this ligament would lessen its power to retain the annulus and the intervertebral disk, which, by its own turgidity and the pressure of the body weight, would tend to be expelled backwards. In addition, the annulus fibrosus itself may sustain damage as a result of its attachment to the posterior ligament. The latter structure is strongest centrally and tends to be much thinner laterally, and as would be expected the majority of disk protrusions are to one or other side of the mid-line. The farther from the mid-line the protrusion occurs the greater the probability of its becoming sequestered in the spinal canal, whereas the more centrally placed protrusions tend to present as smooth bulges behind the ligament.

It has already been pointed out that the pain felt in the lower part of the leg and foot is of a different character from that in the back and thigh. It does in fact bear many points of resemblance to a root pain. It is frequently of a sharp nature, intermittent, referred to the skin, and is often associated with subjective or objective disturbance of sensation. Further, the objective

sensory disturbance lies in the distribution of one of the lower lumbar or upper sacral dermatomes, and is thus compatible with interference with an intraspinal nerve root by a disk protrusion in the lower part of the spinal column. In this connexion it is of interest to note the anatomical relationship of the nerve root to the protrusion. When the latter is medially situated the nerve root is found either on its lateral side or resting on its summit. When the protrusion is laterally placed the root usually lies to its medial side. Owing to the restricted field of view at operation it is not easy to determine which is the affected root, but in 19 of my cases the affected posterior root was divided intradurally. After this there was usually a transitory disturbance of sensation in the cutaneous area supplied, and it appeared that protrusions between the fourth and fifth lumbar vertebrae, although more often involving the fifth root, did sometimes involve the first sacral nerve root, particularly if the disk was medially situated.

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of spasm of the hamstring muscles, since in any circumstances in which these muscles are shortened there is a tendency for the normal lumbar lordosis to be obliterated. A possible explanation of the scoliosis has already been put forward, the primary disturbance being a tilt of the pelvis upwards on the affected side, the scoliosis being compensatory. It must be admitted that this pelvic tilt is not constantly present and some additional explanation is required. It has been suggested that a tilt of the lumbar spine away from the affected side relieves pressure upon the affected nerve root by widening the corresponding intervertebral foramen. This explanation is untenable in the present series as, with one exception, there was no evidence of compression of a nerve root at the intervertebral foramen. Further, a scoliosis convex to the affected side tends to increase the tension upon the nerve roots upon that side. It is suggested here that the scoliosis depends upon a resultant movement of the nerve root away from the summit of the protrusion with a consequent decrease in tension. This would explain the phenomenon of the alternating scoliosis which is occasionally encountered. Further support for the hypothesis that the scoliosis tends to reduce the tension upon the nerve root is gained from the fact that the deformity is frequently more marked in spinal flexion, a movement that is known to increase the tension on the root.

A positive Lasègue's sign is in part an indication of increased tension upon a nerve root, and in part an indication of spasm of the paraspinal and hamstring muscles. O'Connell (1942) has clearly demonstrated that elevation of the extended leg increases the tension upon intraspinal nerve roots, but if this were the sole mechanism operative in the production of Lasègue's sign it would be expected that the pain elicited would be felt in the distribution of the stretched root. This, in fact, is not the case, the pain is usually referred to the back and buttock. Moreover, Lasègue's sign is in part no more than spinal flexion in reverse and as would be expected the pain produced by spinal flexion is similar in character and site to that produced by elevating the extended leg. This sign must be interpreted as indicating primarily damage to ligamentous or fascial structures in the back and to a lesser degree an increase in tension upon an already stretched nerve root. It is, however, more constantly positive in sciatica due to a disk protrusion than in myofascial sciatica and is therefore a sign of diagnostic importance. The neurological signs present result from damage to fibres in the affected root, although flabbiness and wasting of the calf muscles on the affected side cannot be accounted for solely in this way. This latter phenomenon may perhaps be allied to the more profound wasting found in conditions such as osteo arthritis of the knee, in which wasting may precede any limitation of movement and is to be regarded as a trophic disorder. The occasional observation of wasting of the gluteal muscles in sciatica bears out this hypothesis. Diminution of the ankle reflex may be in part due to the hypotonia of the calf, although complete loss of the reflex clearly points to the compressed nerve root as the cause.

The Diagnosis from Fibrositis

The differentiation of sciatic pain due to intravertebral disk protrusion from pain arising from 'fibrositis', so-called myofascial sciatica, is not always easy, and in the absence of neurological signs may be impossible. Certain points of difference arise, however, both in the history and signs. In the present series 110 cases were diagnosed as suffering from myofascial sciatica, of these, two were subsequently found at operation to have prolapsed disks. The average age and the sex incidence did not differ materially in the two groups, but certain predisposing causes were noticeable in the fibrositic group, namely, exposure to dampness and cold, unaccustomed muscular effort, faulty posture, or a tendency to attacks of 'fibrositis'. The faulty posture most commonly associated with the occurrence of sciatic pain was an uncomfortable position while driving a motor vehicle (43 patients in this group were drivers of motor vehicles). A number of these patients complained or had complained of 'rheumatic' symptoms in other parts of the body, particularly in the posterior neck muscles and the muscles of the back of the shoulder girdle. The onset of pain is commonly sudden, often relatively slight at first and tending to increase in severity over a period of hours or days, particularly if immediate rest is not possible. The situation of the pain is variable, but is most commonly felt in the lumbar region, the buttock, and the back of the thigh. Rarely, the pain extends below the knee, and in none of these cases was there any complaint of pain in the ankle or foot. It is usually described as a deep gnawing ache, poorly localized by the patient and tending to be aggravated by movement. Recumbency usually gives considerable relief. The physical signs of this condition are inconstant. The only feature present in every case was local tenderness, usually in the erector spinae or the buttock, and often combined with a diffuse tenderness of the posterior thigh muscles. Some degree of spasm of paraspinal muscles was usually present, but the range of spinal movement present was often surprisingly free. Lasegue's test was positive in 69 per cent of cases, but the result of raising the extended limb differed somewhat from that found in patients with prolapsed disk. The limitation of movement was not nearly so marked and the pain so resulting was felt mainly in the hamstrings rather than in the back or buttock, and was probably to be attributed to traction on muscles in spasm, since this sign can be abolished by the injection of procaine into the site of the primary lesion. In none of these cases was any disturbance of reflexes or cutaneous sensory function observed. Some hypotonia of the calf muscles was noted in 25 cases.

It is clear that differentiation of the early case of disk prolapse from a purely 'fibrositic' condition may be very difficult, the diagnosis resting largely upon negative findings in the latter condition. Further confirmation is forthcoming from the procaine injection test introduced by Steindler and Luck in 1938. These authors suggested five criteria for a proof of the 'fibrositic' origin of the pain.

1. Contact with the needle aggravates the local pain
2. Contact with the needle elicits referred pain
3. Procaine suppresses local tenderness
4. Procaine suppresses referred pain
5. Freedom of leg and spine movement is restored

The essential feature which emerges from these criteria is the abolition of both symptoms and signs by procaine injection into the painful area. This test was carried out in 82 of the present series of cases, the site of injection being into the buttock in 61 and erector spinae in 21. The results were as follows:

Symptoms and signs abolished	64
Symptoms and signs relieved	12
Unaffected	6

It is clear from these figures that the test is valuable in the diagnosis of myofascial referred pain. It is also of interest that there was no recurrence of pain after the injection in 15 of the 82 cases. Injection of procaine into the paraspinal muscles in cases of sciatica due to prolapsed disk frequently resulted in temporary relief of pain in the back, but had no effect on the pain in the leg. Further, but less dramatic, confirmation of the diagnosis was the effect of complete rest. A decrease in the severity of the pain was almost immediate and the majority of patients were free from symptoms within three weeks. Accessory treatment consisted of the application of heat locally during the period of rest, followed by graduated exercises designed to bring about progressively increasing use of the affected structures. By this means 92 cases (84 per cent) were able to leave hospital free from symptoms within eight weeks. Of the remaining 18 cases, 14 were considered to have a functional basis for the continuance of symptoms, and four were discharged from hospital with symptoms relieved but not cured. The cases of symptomatic sciatica in the series do not require further description. The primary disease present was usually obvious, the sciatic pain being only a secondary manifestation.

The Treatment and Prognosis of Prolapsed Intervertebral Disk, with a Note upon the Natural History of Sciatica

The treatment to be adopted in cases diagnosed as having an intervertebral disk protrusion depends upon a consideration of a number of factors. Essentially, two courses are available, conservative treatment, by which is meant complete rest and measures directed toward the relief of individual symptoms, and surgical removal of the protrusion. Firstly, the natural history of sciatica must be considered from the point of view of the possibility of spontaneous cure, the time taken for such a cure if it occurs, and the prospect of relapse. Secondly, on the assumption that cure may result from conservative measures, the question arises whether surgery will materially shorten the time required for recovery. Thirdly, the known results of surgery must be considered with particular attention to the likeli-

hood of permanent cure and the risks, both immediate and remote, of laminectomy. It is difficult to determine from a study of the earlier literature the natural history of sciatica treated by conservative methods. The opinion of Gowers and Taylor (1899) was that sciatica, although subject to relapse and recurrence, was a self-limiting condition, the prospect of eventual cure being good. Wilson (1940) somewhat cautiously stated 'prospects depend on the degree of success with which underlying processes can be treated. On these, too, is contingent the likelihood or otherwise of recurrence.' In Taylor's (1930) *Practice of Medicine* it is stated that the prognosis is 'on the whole favourable. complete recovery is the rule, though in severe cases it may be several months before it is established. There is some liability to recurrence.' More recently Symonds (1938) in the course of a discussion on intervertebral disk protrusions stated, 'Now it is surely true that the great majority of patients with sciatica do get well in the end whatever is done or left undone. the question which naturally arises out of the present discussion is how many patients whose sciatica has been due to prolapsed disk—of course unrecognized—have in the past recovered with rest alone?' Symonds concluded that if prolapsed disk is anything but a very rare cause of sciatica it is a lesion which is capable of spontaneous repair. Speaking at a further discussion on the subject, Symonds (1942) stated that he was not convinced that recovery was materially assisted by operation and that recurrence might equally well occur both in cases treated surgically and those treated medically.

In an attempt to determine the natural history of sciatica the present writer has, in the past two years, asked some 700 persons over the age of 40 years whether they have at any time suffered from sciatica. The majority of the people questioned were hospital in-patients and out-patients suffering at the time from some other condition. Forty-seven of these persons admitted having had at some time a condition diagnosed as sciatica. All but two had had one attack, the period of disability being up to three months. The remaining two cases had had repeated attacks, but not of a severity sufficient to cause great disability. It is realized that the number of people questioned was small and that the diagnoses rested upon the subject's word. Nevertheless, the findings do lend support to the contention that sciatica is a self-limiting disease.

It may be concluded that sciatica is a condition which will recover in the course of time, either spontaneously or as a result of conservative treatment, and it is therefore necessary either to regard intervertebral disk prolapse as a new cause of sciatic pain, which was very rare in the past, a conclusion which is not justified on clinical grounds, or alternatively sciatica due to this cause must be capable of recovery without surgical intervention. It is clear, therefore, that before the question of surgery is considered a prolonged trial of conservative treatment should be made. In cases in which a reasonable trial of medical treatment has been made without relief, or in those in which symptoms reappear immediately upon resuming an active life, the

prospects of surgery must be considered, and it must be asked whether removal of a disk protrusion will result in early relief of symptoms without prospect of recurrence. In this respect the findings of various American writers are encouraging. Love and Walsh (1940) recorded five recurrences in a series of 500 laminectomies and Dandy (1944) referred to 25 recurrences out of 516 cases operated upon. The latter author, however, recognized what he termed a 'concealed disk' which he considered to be twice as common a cause of sciatic pain as the ordinary disk protrusion. These concealed disks are recognized at operation as a cavity in the intervertebral space, it is difficult to understand how a spinal nerve root comes to be compressed by such a cavity. Price (1942) in recording 17 cases of prolapsed intervertebral disk gave a more detailed account of the operative results than is found in any of the American papers on this subject. His results are set out below.

Number of cases	Result			
	Good	Fair	Bad	Uncertain
17	8	4	2	3

These results correspond more closely to those of the present series

Number of disk protrusions removed	92
Immediate relief	64
Improved	17
Unimproved	11

The improvement recorded in the cases in the second category was a relatively gradual process, and it seemed probable that recovery was not greatly accelerated by operation. It will be seen that surgery by no means provides a certain remedy for this variety of sciatica.

Before submitting a patient to operation for removal of a disk protrusion certain criteria must be fulfilled. These criteria are concerned with the duration of symptoms, the response to medical treatment, the nature of the patient's occupation and the prospects of return thereto, and of course the patient's willingness to undergo a major surgical procedure. No patient in the present series was treated surgically if the presenting attack was of less than four months' duration, after four months operation was considered only if medical treatment had been tried unsuccessfully or if relapse had occurred upon resuming normal activity. In those cases in which attacks had occurred at frequent intervals over a period of years, surgery was undertaken only if a period of three weeks' complete rest was without benefit. The question of the patient's occupation is of twofold importance. Firstly, from the economic aspect it is necessary to consider whether surgery will hasten return to work, secondly, the actual nature of the employment, whether sedentary or manual. There can be no doubt that in a case successfully treated by operation an early return to work can be anticipated, with complete freedom from symptoms, whereas further conservative treatment would probably entail a prolonged period of disability even though continued stay in hospital were not necessary. The nature of the patient's employment

is important in that sufficient relief from symptoms may be obtained conservatively for a sedentary occupation to be resumed. A patient engaged in more active work would be more severely handicapped by his symptoms and is more likely to require operation for their relief. In the present series 82 per cent of patients who were treated by laminectomy were engaged in heavy work. The actual risks of operation are very slight, in the present series there were no deaths and the only postoperative complications met were minor sepsis of the wound (7 cases), haematoma at the operation site (4 cases), and a transient retention of urine (11 cases). The remote risks are concerned with the possibility of some disability arising as a result of laminectomy. At the present stage it is not possible to assess the late results of laminectomy, but no disorder directly attributable to the operation has yet been met in any of the cases under consideration. A review of the results of laminectomy five or 10 years after operation is clearly of the greatest importance in this connexion, even though it is known that laminectomies performed for spinal tumours have not given rise to disability many years later. To summarize, the indications for surgical treatment are—symptoms should have been present for four months or longer, medical treatment has failed, economic reasons make necessary an earlier return to work than could reasonably be expected from continued medical treatment, and the nature of the sufferer's work is such that the presence of symptoms debars him from returning to it.

The actual technique of medical treatment requires little description, the essential feature being rest in bed. It did not appear to make any appreciable difference to the results of such treatment, whether freedom of movement in bed was allowed or not. Nineteen cases were placed in plaster beds with the spine in moderate extension. This treatment did not seem to have any particular advantage over unobstructed rest in bed, and had the disadvantage that the majority of patients so treated complained subsequently of some stiffness in the back and legs, and also showed a tendency to develop flat feet. An attempt was made in seven cases to dispense with rest in bed by partial immobilization of the lumbar and lower dorsal spine in a plaster jacket. As was not unexpected, this treatment was uniformly unsuccessful, and all the patients were subsequently treated in bed. No treatment other than the administration of mild analgesics and the local application of heat to the lumbar region, buttock, and thigh was instituted until the symptoms started to abate. At this stage graduated exercises in bed were started, the return of any pain being regarded as an indication that the treatment was progressing too fast, until finally after from three to nine weeks in bed graduated exercises out of bed were commenced. The average duration of stay in hospital for patients successfully treated by this method was eight weeks.

A diagnosis of prolapsed intervertebral disk was made on 163 occasions. Of this total 45 patients received conservative treatment only. On leaving hospital 29 were free from symptoms, 12 were much improved, and four

were unimproved but refused operation. Of the 41 patients either symptom-free or relieved, seven were civilians, all of whom were able to resume their normal occupations. Of the remaining 34 Service patients eight were considered unfit for further military service and were discharged. Twenty-six returned to Service life in a low medical category. Only one of the civilian patients has since complained of a severe return of pain, and a further period of rest resulted in complete relief of symptoms. Unfortunately, a follow-up of the Service patients in this group has not been possible.

It is beyond the scope of the present paper to describe in detail the operative technique employed in removal of intervertebral disk protrusions, but the methods of all six surgeons concerned with these cases were broadly the same. In general the operation consisted of removal of the spines and laminae of the fourth and fifth lumbar vertebrae, the minimum of bone being removed compatible with an adequate exposure. In the course of removal of the laminae the ligamenta flava were resected as far laterally as the lateral intervertebral joints. The more laterally placed 'sequestered' disk protrusions were usually visible without retraction of the dural sac. The medially placed protrusions were usually revealed only after retraction of the dura. The disk material was removed extradurally in all cases except one, the latter, one of the four having centrally placed disk protrusions, had had a lipiodol examination made, and opening of the dural sac was necessary for removal of the oil. Mention has already been made of the varying relationship of the affected nerve root to the disk protrusion. It was an interesting feature, in marked contrast to the findings of other writers, that in spite of the apparent tension existing in the affected nerve root, the root itself appeared quite normal in size, colour, and consistency in almost every case. Removal of the sequestered type of protrusion was a very simple matter. Usually a small incision into the thin ligamentous covering was all that was required to enable the protrusion to be lifted out intact. Removal of the medially placed disk 'bulge' was more difficult, the disk material having to be excavated piecemeal. The dural sac was opened only when removal of iodized oil was necessary, or when division of a posterior root was intended. Removal of the disk protrusion, in some cases with division of the affected posterior root, was, with one exception, the only operative procedure carried out in the present series of laminectomies. In this particular patient no abnormality was detected, and in view of the very severe nature of the symptoms and signs in the back a bone-grafting operation was performed with subsequent very good effect, the symptoms being completely relieved.

In 26 of the operations performed no disk protrusion was found, and it is noteworthy that in 15 of these cases the symptoms were confined to the back, buttock, and thigh. In two cases definite disturbance of sensation was observed before operation, and in seven there was doubtful impairment of perception of pin-prick over the lateral part of the dorsum of the foot. In 12 cases the ankle reflex was diminished on the affected side, and was asso-

ciated with marked hypotonia of the calf. At operation 11 patients were found to have very marked thickening of the ligamentum flavum on the affected side, and in three the thickening was bilateral. Only once was any mechanical interference with a nerve root found. In this case a large osteophytic outgrowth was detected and removed from behind the right fifth lumbar nerve root. Symptoms were subsequently only partially relieved, and the patient continued to complain of pain in the back and thigh, although the pre-existing pain in the leg and foot had ceased. In none of the other cases was any evidence of root compression detected. It was not considered that the thickening of the ligamentum flavum could in itself compress the nerve root even at the intervertebral foramen, and it can only be assumed that these cases were examples of myofascial sciatica, in which the history, symptoms, and signs resembled those characteristic of prolapsed disk. Of the 26 cases referred to above, seven were immediately relieved of all symptoms by operation, 16 made a gradual recovery, and three were unimproved six months after operation. Of the 23 that improved, 12 have been observed for from six to 18 months and none has relapsed so far.

The post-operative treatment differed only in minor details at the various hospitals concerned. For the first three days after operation the patient was not encouraged to make any attempts at movement. Position was changed two-hourly and lying on the back encouraged. It is remarkable how comfortable patients usually were in this position, in spite of the wound in the back. A careful watch was kept for any disturbance of sphincter control, in particular retention, for which condition catheterization was occasionally necessary for 24 to 48 hours. From the fourth to the tenth day, if the patient's general condition permitted, passive movements of the legs were commenced, active movements being encouraged as soon as they could be painlessly performed. From the time of the removal of stitches on the tenth day a course of graduated exercises in bed was instituted and maintained until the patient was allowed to get up on the twenty-first day. Initially patients were allowed up on the fourteenth or fifteenth day, but this was followed so frequently by a complaint of backache that a further week in bed was considered advisable. From the fourth until the end of the fifth or sixth week increasing activity was encouraged with graduated exercises and the successful cases were allowed to leave hospital at the end of this period, the Service patients being placed in a low medical category for six months, and the civilians forbidden any violent exertion for three months. Civilians normally engaged in heavy work were advised to obtain lighter employment for the first three months.

Two important facts in connexion with prognosis arise from the operative technique and findings: Firstly, in the majority of the laminectomies care was taken to avoid injury to the lateral intervertebral joints and their capsules, but in 35 cases adequate exposure at operation made some encroachment upon the joint on one or both sides necessary, and in these the incidence of post-operative backache and stiffness, particularly in flexion,

was very high (40 per cent) Where no encroachment upon the joint was made an almost full range of spinal movement was present by the twenty-first day, and the general rate of cure was higher in the latter than in the former group Secondly, the variety of disk protrusion had a considerable bearing on the subsequent course The finding of a sequestered protrusion was usually followed by rapid recovery, whereas the finding of a medial bulge which had to be removed piecemeal was followed by a much less dramatic improvement, if indeed any improvement took place, and was more likely followed by a relapse subsequently

Disk protrusion		Result of operation	
Medial	36	Complete cure	64*
Sequestered	51	Improved	17
Mid line	4	Unimproved	11
Extreme lateral	1		

* Immediate relief, 42, gradual improvement, 22

Of the 42 patients immediately relieved by operation all had sequestered disk protrusions The remaining 11 patients with protrusions of this type made a full recovery within three months of operation Two of the cases with mid-line protrusions were immediately relieved, and also the one case of extreme lateral protrusion

From a consideration of the results of the surgical treatment of prolapsed intervertebral disk one important fact emerges The only constant result of surgery is the relief of the symptoms and signs of involvement of the spinal nerve root When symptoms persist post operatively they are almost always confined to the back, buttock, and thigh Pain in the lower part of the leg and foot is no longer present In the 17 patients in which improvement was noted, the residual symptoms were of pain and stiffness in the back and thigh, and no complaint of pain in the leg was made This also applied to those cases in which gradual improvement eventually led to complete cure This finding again points to the fact that the disk protrusion is only a part of a much more widespread pathological process of the lumbar spine Post-operatively, the majority of the signs associated with intervertebral disk prolapse disappear rapidly in successful cases The orthopaedic signs are usually minimal by the time the patient is allowed out of bed, although some slight limitation of spinal flexion may persist for some months Straight-leg raising is not usually full for three to six weeks—an indication that the basis of Lasègue's sign is not solely a question of applying tension to the lower spinal nerve roots Any sensory disturbance present before operation usually regresses rapidly and is not usually detectable three months after operation Tone returns to the calf and gluteal muscles rapidly, and often these muscles appear normal by the time the patient is allowed up, unless a marked degree of wasting has been present The ankle reflex, if only diminished previously, usually becomes normal within a few weeks An ankle reflex that is once completely lost seldom returns

In order adequately to assess the results of treatment of this kind of

sciatica it is obviously necessary to keep the patient under observation for a very long period, perhaps even 10 years. The result of observations of the present series of cases must therefore be regarded as a preliminary survey, since three years is the maximum time that has elapsed since the first was treated surgically. Added to the time factor there is the difficulty of maintaining contact with patients after they have left hospital. Of the 81 patients cured or improved on leaving hospital, it has been possible to observe 66 for periods varying from six months to three years. Six of these patients have had relapse with return of their original symptoms and signs. In each of these six cases a medial 'bulge' has been found at operation.

Sixty patients had no relapse in the periods shown below

6 months	1 year	18 months	2 years	3 years
29	21	4	4	2

All the 25 civilians in this group returned to their previous occupations. Of the remainder, 15 remained in the Services, the majority in a low medical category, and 20 were graded unfit for further active service and returned to their peace-time employment.

The immediate rate of cure after surgical removal of a prolapsed intervertebral disk was 69 per cent. No accurate figure can be given for the percentage remaining cured after six months, owing to the fact that it has not been possible to follow the progress of all the cases. At six months the number that were symptom-free was in the neighbourhood of 74 per cent, and this figure includes those cases in which improvement was a gradual process. Only four of the 11 cases that were unimproved were subsequently seen. Two were somewhat better. In all four well-marked signs were still present in the spine, but no evidence of root involvement was detected other than an absent ankle reflex in one case and a diminished ankle reflex in three. Division of the posterior root did not seem to have any material effect on the prognosis.

Since the analysis of the cases here recorded was made, Burns and Young (1945) have published the results of operation in 177 cases, some of which are included in the present series. Their figures show an improvement which is ascribed to the more complete removal of disk material in those patients more recently subjected to operation.

Summary

1. An account is given of the symptoms, physical signs, and treatment of a number of patients suffering from sciatic pain.
2. Trauma plays an important part in the production of an intervertebral disk prolapse, but has little relevance to the myofascial type of sciatica.
3. The symptoms of intervertebral disk prolapse may be divided into two stages, the stage in which pain is confined to the back, and the stage in which pain is also present in the leg. Remissions are characteristic and are largely independent of treatment.

4 The symptoms of myofascial sciatica are less constant, but the diagnosis from pain due to a disk protrusion may be impossible in the early stages of the latter condition

5 The characteristic physical signs of intervertebral disk protrusion are described. They fall into two groups, the mechanical and the neurological. The former are mainly due to changes in ligamentous and fascial structures in the lumbar spine, the latter are due to pressure upon the nerve root by the disk protrusion itself.

6 Surgical treatment of prolapsed disk is by no means certain to result in cure, certainly not immediate cure, and in some cases it is doubtful whether the slow improvement which results is directly attributable to surgery. From these results it would also seem justifiable to assume that removal of the protrusion itself will only relieve the symptoms of root compression, the relief of myofascial symptoms depending upon the removal of other affected structures in the course of the operation and perhaps upon the process of repair stimulated by the trauma incidental to the operation.

7 It is the writer's opinion that surgery should be reserved for those patients in whom prolonged rest has failed to give relief or for those in whom economic reasons render the prospect of a rather more speedy return to work desirable. Further, it is considered that a history of pain in the back and thigh without evidence of root compression does not alone constitute sufficient grounds for the performance of laminectomy, although a disk protrusion may be found in such cases, there is insufficient evidence to show that it is the primary cause of symptoms.

8 A comparison of the results of conservative and operative treatment of intervertebral disk prolapse leads to the suggestion that caution should be exercised in recommending the latter course. In addition there is reason to believe that sciatica, with the exception of the symptomatic variety, is a self-limiting disease, and that operation is practically speaking only a short cut in an otherwise tediously protracted disease.

The surgeons concerned in the operative treatment of these cases were Mr B H Burns, Mr R H Young, Mr Harvey Jackson, Mr E B C Hughes, Mr H L C Wood, and Mr R H Boggon, to all of whom the writer expresses thanks for permission to utilize their case notes and record their operative findings.

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FAINTING AND FLYING

AN ANALYSIS OF 500 CASES OF IMPAIRMENT OF CONSCIOUSNESS IN PILOTS AND AIRCREW¹

BY A F ROOK

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THE seriousness of loss of consciousness occurring in members of a flying service needs no emphasis. The condition presents one of the most difficult problems facing a Medical Officer in the Royal Air Force, and one in which correct diagnosis and disposal is of prime importance. Before the war a number of cases of fainting had been studied, but they were comparatively few. The conditions of war and the expansion of the Royal Air Force caused a considerable increase in the number of patients complaining of these symptoms.

Material and Scope of the Investigation

The series consists of 500 patients all of whom were seen at the Central Medical Establishment. Instructions were given that all pilots and aircrew complaining of attacks of loss of consciousness of any sort were to be reported. By this means the whole series was collected during a period of about two and a half years. No attempt has been made to select the cases, they have been collected consecutively as they attended at the Central Medical Establishment. It is not suggested that every case occurring during the period of observation has been included, in some instances the symptoms may have been incidental and not mentioned in the history. With constantly changing personnel, some of whom may not have realized exactly what was required of them, cases must inevitably have been missed, but it is not thought that the number missed can have been large. All difficult and obscure cases tend to gravitate eventually to the Central Medical Establishment, a fact which to some extent alters the balance of the figures. Medical Officers of units or hospitals may themselves deal with obvious cases of slight character, but when temporary or permanent 'grounding' is likely the patient is nearly always referred to the Central Medical Establishment. In most instances the patients were seen and examined personally, but in my absence the papers were kept and shown to me as soon as possible after my return.

All forms of sudden or moderately sudden disturbance of consciousness or awareness are included, ranging from conditions of amnesia, confusion, transient giddiness, or dizziness to complete loss of consciousness with or

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without convulsions. Straightforward cases of vertigo due to aural conditions or of giddiness associated with airsickness were normally omitted. If there was any doubt as to the diagnosis, the case was included. Patients who had loss of consciousness immediately after an accident, and due to the accident, were excluded. Besides a complete clinical examination, in almost every case a neuropsychiatric opinion has been available. The great majority of the patients had a routine X-ray of the chest and an electrocardiogram done. In well over half an electroencephalogram was taken, in nearly every instance at the Centre for Head Injuries at Oxford, and reported on by Wing-Commander Denis Williams. A number of cases were tested in the decompression chamber at the Royal Air Force Physiological Laboratory at Farnborough, where blood-gas and other estimations were done. In a few instances, tests for sensitivity to centrifugal forces were carried out.

For the purpose of analysis all flying personnel in the Royal Air Force have been divided into those actually flying the aeroplanes, the pilots, and all other members of the flying branch, navigators, bomb aimers, flight engineers, and others, who have been classed as aircrew.

With such a large subject it is impossible to do more than indicate a few points which seem specially to bear on classification and diagnosis.

Classification

It is usual to discuss sudden transient giddiness and loss of consciousness under two heads, those cases due to an increased sensitivity of the nerve elements and those associated with changes in the blood-supply to the brain. So far as Aviation Medicine is concerned, this classification is insufficient to include all the cases seen, and it is imperative to take more account of those emotions and spheres of mental activity that form the highest levels of consciousness. During flying, particularly operational flying, the various emotions, specially anxiety and fear, play so large a part that consciousness may be affected with little or no apparent involvement of the nerve-cells of other levels or of the other bodily mechanisms. Those affected in this way are as much out of touch with their surroundings and with what is happening as if they were unconscious. They may perform certain automatic acts, but these acts are akin to those of a decerebrate animal. Some observers would class the attacks under the heading of psychomotor seizures or psychic equivalents (Lennox, 1941), but it seems best until further knowledge is available to put this type of case into a separate class. Thus, in the analysis which follows, three separate mechanisms are believed to form the basis of the pathological processes which lead to the attack. Firstly, disturbances of the highest cortical levels, secondly, a hypersensitivity of the nerve-cells at a lower level leading either to explosive discharge or to pathological inhibition, and thirdly, alterations in the quantity or quality of the blood-supply to the brain. This classification follows that suggested by Romano and Engel (1945), who showed that electroencephalograph records taken

during actual loss of consciousness fall into three groups, the emotional type of fainting, the epileptic type, and the syncopal or vasodepressor type

However much outside influences, specially those working through the blood supply to the brain, appear to be causal, it must not be forgotten that the essence of all loss of consciousness must be some change in the nerve-cells themselves, whether brought about by mechanical, chemical, or electrical agencies. It is rarely in any given case that only one of these pathological processes is at work. The interrelation of the various factors causing the attack is often so complex that it is quite impossible to separate them. Emotion may be the trigger that unlooses an epileptic fit or causes an attack of syncope (Penfield and Erickson, 1941). Epilepsy and cardiovascular syncope appear to have a common meeting-place in the brain (Gowers, 1907). Attacks grade gradually from pure cardiovascular syncope to pure panic states. Postural giddiness is usually considered certain evidence of cardiovascular inefficiency, yet Gowers has reported a case where sudden rising from the sitting position induced epileptic attacks. Others have described cases where repeated syncopal attacks have gradually taken on an epileptic character, and have noted the marked tendency in epileptics to vasomotor instability, indicating that the line between fainting and fits cannot be sharply drawn. The necessity of placing any individual case in a particular group tends to obscure the multiplicity and complexity of the many factors which are almost invariably present. In classification one has to try to estimate which factor is of predominant importance without forgetting that more than one has probably been at work.

Diagnosis

One of the great difficulties in dealing with this type of case is that only rarely is the doctor able to witness an attack. It is therefore necessary to rely on the patient's story, with possibly a statement from a lay witness, objective evidence is absent or at most slight.

Past history A history of previous attacks of loss of consciousness, with a knowledge of the attendant circumstances, is often of the greatest value in diagnosis. On entry to the Service each candidate for flying duties is questioned about fainting attacks. In addition he signs a certificate stating that his answers are complete and correct, and that he has not withheld any relevant information or made any misleading statements. Unfortunately, little reliance can be placed on the history given by the candidate at this time. In the present series of cases a personal history of fits or faints was given on entry by 25 patients, subsequent to the attack 154 stated that they had had fits or faints before joining the Service.

Psychiatric examination The importance of a psychiatric examination in each case cannot be over-estimated. The degree of predisposition to neurosis, the amount of flying stress to which he has been subjected and his reactions thereto, and worry and anxiety apart from flying, all require investigation and assessment. From these angles most help can usually be obtained in

coming to a diagnosis and deciding disposal. Often it is not what occurs during an attack that is of most importance, but the circumstances in which the attack occurred and the mental state of the patient beforehand.

Associated factors In the ensuing analysis a number of cases has been separated in which attacks of loss of consciousness have occurred in association with organic disease. Often there seems little doubt that there was at least some relation between the disease and the symptoms, but it is only too easy to ascribe an attack to some incident or pathological process to which actually it has been entirely unrelated. Because a patient shows evidence of nerve-cell hypersensitivity it does not mean that every attack of unconsciousness from which he suffers is necessarily due to this cause. The epileptic may have a syncopal attack, the man with cardiovascular instability may suffer from epilepsy. A stimulus which in one may cause syncope may in another cause epilepsy (Brain, 1940).

Despite uncertainty, some questions require an immediate if tentative answer, so that decisions as to disposal can be made—what is the most likely basis of the attack, should the patient be permanently or only temporarily 'grounded' with the hope of eventual return to flying, was this an isolated incident, and what is the likelihood of recurrence of the attack? Obviously the safest course would be to 'ground' these patients permanently, but such a course, apart from meaning the loss of skilled men who have taken months or years to train, may mean the sudden loss of livelihood with no other training on which to fall back. It is as unfair consistently to play for safety as it is to take risks, knowing that not only the life of the patient but of others may depend on the decision.

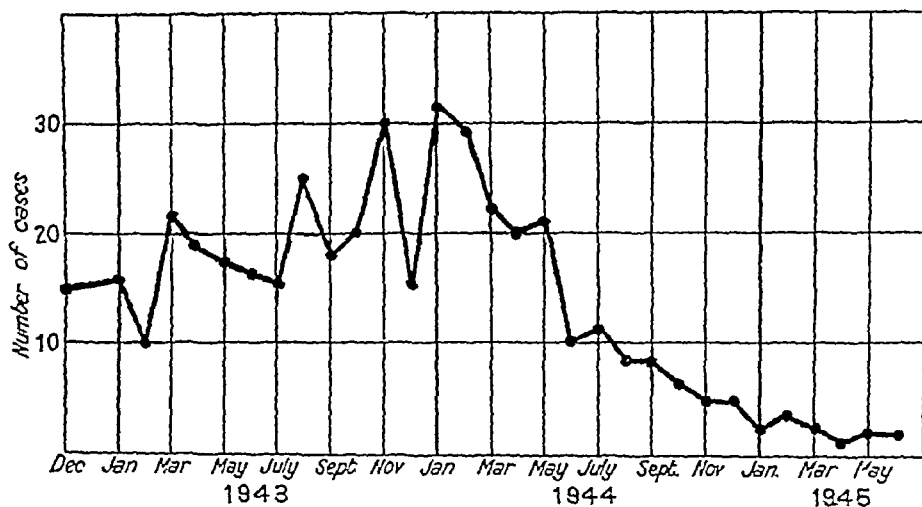
Numbers Of the 500 cases, 121 (24 per cent) were regarded as primarily neurogenic, 154 (31 per cent) as primarily due to some cardiovascular cause, and 208 (42 per cent) as primarily emotional in origin. There was so much doubt as to the origin of the remaining 17 (3 per cent) of cases that they have been left unclassified.

Occurrence There was considerable variation in the numbers seen each month, at one time during the winter of 1943-4 on an average just under one fresh case was seen every day (see Figure). With the preparations for the invasion of Europe there was a marked drop in numbers, with a steady decrease till the end of the war with Germany. It is possible that more cases were being missed during the latter half of 1944 and the first part of 1945, but it is not thought that enough slipped through to alter the shape of the curve materially. This fall in incidence, immediately preceding and during the invasion of Europe, paralleled the fall in incidence of psychiatric cases in the Royal Air Force which was noted by a number of observers. It shows the predominating part that psychological influences play in the production of the type of case under consideration. As a German General remarked about the campaign in Poland, 'Men of a conquering army do not report sick.'

Grading The series included more members of aircrew than pilots in a ratio of about 3.5 to 2, but as during the period in which these cases occurred

the general ratio of aircrew to pilots averaged 6 to 2, it seems that pilots are more likely to be affected than aircrew. The incidence of neurosis among aircrew and pilots given by Symonds (1945), 4 to 2, lies between these two ratios, again showing a preponderance in pilots but not quite so markedly.

Location of attacks The number of attacks reported as occurring solely in the air was 118, solely on the ground 263, and both in the air and on the



The date of onset of symptoms in the Royal Air Force in the 500 cases of impairment of consciousness among pilots and aircrew

ground 119 cases. In each group the proportion of pilots to aircrew varied little and there is nothing to bear out the suggestion that pilots are affected more in the air than are aircrew.

Cases Regarded as Primarily Neurogenic

The definition of the term epilepsy has troubled many generations of doctors and no wording has yet been universally acceptable. In the present analysis the word is used only for attacks which are usually designated as idiopathic epilepsy. The view here taken is that in this group the attacks of loss of consciousness result from disturbance beginning in the neurones, the excitability of the neurones varies with different individuals and from time to time in the same individual. In addition to this constitutional factor there is often a precipitating factor, which may be of so varied a nature and is often of so opposing a character, that it must act by increasing the susceptibility of the neurones (Cobb, 1936). One factor which may act in this way is emotion and it is one that is of special importance in attacks occurring in flying personnel. According to this view everybody is liable to epileptic attacks, in some the affected neurones are so irritable that attacks occur spontaneously or from causes so slight as to be inappreciable. At the other end of the scale the constitutional tendency may be so small that the precipitating stimulus must be of the most severe nature.

TABLE I
Cases Regarded as Primarily Neurogenic

Number of cases	Rank		Trade		Location of attacks			Disposal					
	Officers	Other ranks	Pilots	Aircrew	Under training	Air only	Ground only	Air and ground	Permanently unfit for flying	Full flying	Limited flying	Full aircrew duty	Temporarily unfit for flying
121	44	77	35	99	17	6	93	22	109	5	2	5	0
9	4	1	2	3	0	1	3	3	5	0	0	0	0
9	5	4	6	2	1	3	3	4	1	1	0	0	0
13	5	8	4	8	1	0	12	2	12	0	0	0	0
5	3	2	1	4	0	1	2	2	5	0	0	3	0
20	3	17	3	13	4	0	20	0	17	0	0	0	0
10	4	6	3	5	2	0	7	3	10	0	0	0	0
6	2	4	3	3	0	1	4	1	6	0	0	0	0
93	18	35	13	31	9	0	44	9	53	0	0	0	0

Number of cases

Diagnosis (see Table I) Theoretically there is a clear difference between the epileptic fit, the syncope attack, and the attack of psychogenic origin. Practically this is far from being the case. Epilepsy may be characterized not by convulsions but by flaccidity, while convulsive movements are often seen in syncope. When occurring in syncope these convulsive movements, which may vary from a few twitches to comparatively violent movements, are too often taken as evidence that the attack is epileptic in nature. It is difficult to obtain figures of the incidence of convulsive movements in syncope, but they are far from uncommon. In the Medical Research Council Report (1944) over 50 per cent of blood donors who fainted had convulsive movements, an incidence very similar to that reported from the United States of America by Boynton and Taylor (1945). The incidence of convulsive movements in the cerebral anaemia of the Stokes-Adams syndrome is high and bears a definite relation to the length of the asystole (MacKenzie, 1918). Cowan and Ritchie (1935) stated that if standstill of the ventricle lasts for 10 seconds or more convulsions both tonic and clonic usually supervene, they described three patients all of whom had convulsions, two with marked cyanosis, and one with frothing at the mouth, all were dazed after the attack. Convulsions occurred in five of eight cases reported by Parkinson, Papp, and Evans (1941), one patient having incontinence of urine. Rosen, Kabat, and Anderson (1943) have shown, by means of a device with which they could almost instantaneously arrest the cerebral circulation, that convulsive movements invariably followed sudden stoppage of blood-flow to and from the brain. The movements occurred after the circulation had been allowed to resume and their severity and duration depended, within certain limits, on the period of arrest of the cerebral circulation.

In the 379 cases thought to be due to cardiovascular, psychological, or doubtful causes, 34 were reported as having convulsions, varying from slight twitching to violent struggling. In nearly every instance a diagnosis of epilepsy was made or was seriously considered. There can be no doubt that the more nearly the description of an attack corresponds to that usually accepted as typical grand mal, the more likely it is to be epileptic in origin. Yet there is much justification for Weiss's (1940) contention that there is no symptom or combination of symptoms that occur in a grand mal attack that cannot also result from cerebral anaemia. The occurrence of twitching or even major convulsions in association with loss of consciousness does not justify a diagnosis of epilepsy on these grounds alone.

Major idiopathic epilepsy The number of cases thought to be definitely epileptic in origin was 53, there were six others which were almost certainly epileptic, but about which some doubt had been expressed, making 59 in all. Another 46 patients were regarded as possibly suffering from epilepsy, but there was considerable doubt and they have been included in other groups. All except three were below 30 years of age. A history was obtained of attacks during sleep in 17 patients, biting the tongue in 13, involuntary micturition in nine, and incontinence of faeces in four. In five instances the

attacks appeared to be related to heavy drinking, possibly the excess of fluid or possibly the alcohol being the precipitating factor, the attack usually occurred during the night or on the morning after the excess. Of interest in this group was a case of epilepsy with a history of repeated syncopal attacks earlier in life.

A Flight-Sergeant Navigator aged 26 years had done 230 hours flying, none of which was operational. At school he had always been prone to faint, at the age of 11 years he had fainted on a parade and he always felt nauseated and faint on hearing of injuries or wounds. In 1941 he developed an anxiety state after being rejected from a pilot's course. A week later he had a feeling of nausea, followed by an attack of unconsciousness in which he fell and broke his nose. Two years later he had an attack with tonic and clonic phases and frothing at the mouth, he regained consciousness quickly but was dazed for some period. An electroencephalogram was reported as showing a larval epileptic seizure. The original attacks were regarded as syncopal, the two later ones as epileptic.

Minor idiopathic epilepsy A diagnosis of petit mal was made in 10 cases.

A Pilot Officer, aged 28 years, had done 1,500 hours flying, chiefly as an instructor. While at the University he had joined the Air Squadron and had flown for about two years. During this time he had attacks of petit mal at irregular intervals, sometimes a fortnight elapsing between attacks, sometimes a dozen or more occurring in an hour. He saw a doctor who diagnosed the condition and he left the Air Squadron. He joined the Royal Air Force in 1941, carefully failing to answer the question about fainting attacks on the form of entry. The attacks persisted all the time he was instructing, but despite this the Chief Flying Instructor reported that he was 'utterly normal in every respect—he is a very good and capable instructor'. The climax came when he took up a machine with which he was unfamiliar, and had an attack lasting some seconds, recovering to find himself heading directly into the middle of a lake. He was extremely frightened after this experience and reported sick. An electroencephalogram showed larval epileptic attacks.

Single convulsive attacks In 20 instances a single convulsive attack was reported. In eight cases the tongue was bitten, in three there was involuntary micturition, and five attacks occurred during sleep. A history of taking excess of alcohol was given in six cases, the drinking usually preceding the attack by several hours. In one instance the convulsive attack took place a few hours before the onset of an attack of pityriasis rosea, in another it occurred during sulphonamide treatment of gonorrhoea when a considerable quantity of water was being taken. Epilepsy may start in adult life and hence the attack in question may be a first attack, but 'a single attack does not justify a diagnosis of epilepsy with all its attendant concern and anxiety' (Gowers, 1907).

Cerebral neoplasm Five patients were diagnosed as having intracranial lesions after investigation at the Centre for Head Injuries at Oxford, but in no case has the diagnosis yet been confirmed.

Convulsive attacks after injury occurred in 13 instances. In each case it was after severe injury directly affecting the head, fracture of the skull-bones being reported in six of the patients.

Vertigo of aural origin These cases are included in the series as there was some doubt as to the diagnosis, and they were sent to the medical and neurological departments. In all nine cases the symptoms were regarded as due entirely to the aural condition.

Miscellaneous cases One officer had a convulsive attack due to cerebral syphilis, and there were four examples of abnormal sleep states. Two of these were thought to be cases of narcolepsy and the remaining two were of more doubtful origin.

Of the latter, one, an Instructor, disliked night flying and got into a state of complete indifference even in situations which he knew to be potentially dangerous. This indifference associated with fatigue led at times to a state of drowsiness, or even sleep, so that on more than one occasion the machine was out of control and he and his pupil in serious danger.

The other occurred in an Air Gunner aged 23 years with 250 hours flying to his credit, of which 100 hours (15 sorties) were operational. His father was Irish and his mother French. As a child he was erratic in temperament, unafraid, and constantly fighting. He was easily aroused to anger but could control his temper fairly well. His whole adult life was spent in a restless craving for excitement, but he soon became intolerant and bored. He had been a barman and at times drank heavily. He joined the Royal Air Force on impulse and after several months on ground work he volunteered to become an air gunner. After the first few trips when the novelty had worn off, he invariably went to sleep during flights. This began to happen on operational flights so that he was asleep practically the whole time except when over the target, and he was often asleep even there. The only time he seems to have been fully awake was when they were being attacked by night fighters. On one sortie it was reported—'this Flight Sergeant was supposed to be in the blister watching for enemy fighters. While walking along the aircraft I unexpectedly found him sleeping, lying beside the compass. I shook him twice but he did not wake. He awoke when his face was slapped just as we were over the French coast on the return journey.' Caffeine and benzidine seemed to have but little effect, and the Medical Officer reported that no one wanted to fly with him. No satisfactory diagnosis could be suggested.

There was no evidence of a cerebral neoplasm in any of these cases, all four were of big build, being considerably too heavy for their height.

Incidence of epilepsy among pilots and aircrew The number of cases in this section totals 121, of which 69 are regarded as due to idiopathic epilepsy. One cannot escape the impression that in a selected community who have twice been through careful medical examinations the numbers seen are larger than would be expected. In the general population, would a series of 500 cases of impairment of consciousness of a like type in young adults include so high a proportion as over 1 in 8 of idiopathic epileptics? To get truly comparable figures is, however, well-nigh impossible. It is probable that a number of minor cases of giddiness and dizziness never reach the Central Medical Establishment, but are dealt with by Station Medical Officers so that the actual incidence of epilepsy is lower than our records seem to show. In Table II the figures for epilepsy and 'observation epilepsv'

(that is, all patients referred to the Central Medical Establishment with a confident diagnosis of epilepsy or where the diagnosis, while doubtful, was considered probable) occurring in the whole of the pre-war Royal Air Force are compared with similar figures occurring among pilots and aircrew reported during 18 months when severe operational flying was taking place. These figures show an increased incidence among the flying personnel. The problem

TABLE II

Comparison of the Number of Cases of Idiopathic Epilepsy and 'Observation Epilepsy' occurring among Pilots and Aircrew 1943 and the first half of 1944 with the Number occurring in the whole of the Royal Air Force before the War

PRE WAR ROYAL AIR FORCE (ALL RANKS)

Year	Average strength	Number of cases of epilepsy and 'observation epilepsy'	Incidence of cases per 1,000 of strength per annum
1932 to 1936	35,260	Average 17.8	0.5
1937	59,532	43	0.7
1938	76,300	45	0.6

PILOTS AND AIRCREW ONLY

1943	40,600	53	1.3
1944 (first half)	47,000	25	1.1

bristles with difficulties, including the fact that the flying personnel population differed in age grouping from the pre-war Royal Air Force and was of a floating type, the pre-war Royal Air Force population, while floating to some degree, was considerably more static. There does appear to be an increase, but how far it is significant is difficult to say. If this increase is really true it may well be that the influence of emotion in causing epilepsy in apparently stable individuals is greater than is generally supposed. This hypothesis received some confirmation from the fact that withdrawal from flying duties was almost invariably followed by cessation of attacks in those cases where it has been possible to obtain a subsequent history. It would have strengthened the case if the incidence could have been shown to have been highest in the crews of bomber aircraft, for Symonds (1945) has shown that they are the most prone to neurosis. Actually the highest incidence was in those doing flying training, only 18 out of 69 having done any operational flying.

One factor which certainly had an influence in the production of epilepsy was the frequency of hyperventilation of emotional origin in pilots and aircrew. Hyperventilation may act in a number of ways in the production of attacks of unconsciousness, and one of these is its well-known effect in producing epileptic attacks. This subject is discussed in its relation to attacks of syncope in a subsequent section.

The high incidence of epileptic attacks found in the present series is not so high as that found by Williams (1945) in 100 cases of unconsciousness, confusion, and amnesia in pilots and aircrew seen at the Centre for Head

Injuries at Oxford The principal reasons for the differences are that Williams confined his attention to patients whose attacks occurred in the air. In consequence his figure for so-called vasovagal attacks is extremely low, for they occur infrequently in the sitting position. There was also a natural tendency to send to Oxford patients in whom an electroencephalographic examination might be of help, while if the clinical findings pointed strongly to a cardiovascular origin the patients were often dealt with at the unit or the Central Medical Establishment. Williams's cases were therefore highly selected, thus accounting for his high figure of 32 per cent for epilepsy.

Cases Regarded as due to Alteration in the Quantity or Quality of the Blood-supply to the Brain

In the common type of syncope the main objective finding is a sudden fall in blood-pressure, but how this is produced and why unconsciousness results is far from clear. It is usually assumed that the fall is due to loss of control of peripheral arterial tone by the vasomotor centre. Recent work by Barcroft and Edholm (1945) has shown that the drop in arterial blood-pressure is probably due not to any loss of control, but to active vasodilatation in the arterioles of all skeletal muscles, while cardiac output and intra-auricular pressure are often substantially unchanged, or may even be increased. No satisfactory explanation has been given why a drop in blood-pressure to a level that may be normal or usual for some people will often cause a loss of consciousness. Despite the sensitivity of the brain-cells to anoxia there seems no obvious reason why rapidity of fall is so essential to the loss of consciousness. As older writers have pointed out, the nerve-cells are bathed not in blood but lymph, and it seems unlikely that nutritional substances can be used up or metabolites accumulate in so short a time. Possibly the sudden alterations in pressure within the cranium may have more effect than is commonly supposed. It is little to be wondered at, in view of this uncertainty, that attempts to obtain objective clinical evidence of a liability to syncopal attacks meets with so little success.

Diagnosis (see Table III). The majority of syncopal attacks are associated with an underlying increase of emotional tension, and are omitted from the section. In airmen in war-time a state of nervous tension is common, in some the nerves may be persistently taut to the last degree, so that some apparently irrelevant word or sound may produce the extra pull necessary to reach the breaking point. Almost inevitably the patient will try to explain away the attack as the result of some slight injury or indisposition, seeking to hide the real cause. Herein lies the importance of the psychiatric examination, in every case of syncope an estimate of the nervous tension and the stress under which the subject is labouring should be made during the examination. Other cases are associated with a liability of the vasomotor system which may fail to sustain an adequate flow of blood to the brain in the absence of any superadded emotional element. This is specially

TABLE III
Cases Regarded as Primarily Cardiovascular in Origin

Diagnosis	Rank		Trade		Location of attacks		Disposal				Total	
	Officers	Other ranks	Pilots	Aircrew	Under training	Air only	Ground only	Air and Ground	Permanently unfit for flying	Partially flying		Full aircrew duty
Haemorrhage	2	3	2	3	0	0	5	0	0	1	3	0
Infection	11	14	16	9	1	3	18	4	10	5	4	2
Pain	4	3	5	2	0	4	3	0	0	0	2	0
'Blackout'	2	5	3	3	1	7	0	0	5	0	4	0
Organic heart disease	3	7	4	5	1	1	6	3	9	0	1	0
Fatigue	10	3	3	3	7	2	11	4	3	6	7	0
Heat	18	10	8	5	2	3	6	7	5	5	4	0
Hypotension	15	9	8	5	2	2	15	2	12	3	2	0
Cardiovascular inefficiency	19	9	11	6	2	2	26	4	20	7	4	0
Miscellaneous	31	19	14	14	3	1	7	3	6	2	5	0
	17	8	6	11	0	7	7	3	6	2	4	0
Total	154	87	76	61	17	30	97	27	70	34	32	4

likely when some factor which acts adversely on the blood-pressure, such as fatigue or minor infection, is also present. It is these cases, where emotion has played but little part, that are classified here.

Although physical efficiency tests may show evidence of cardiovascular inefficiency, there are many difficulties which often render the results useless. More young adults show evidence of cardiovascular inefficiency than suffer from syncopal attacks, the instability may only be of a temporary nature, and by the time the patient comes for examination objective evidence may be lacking. There can be no doubt that great care is required before any conclusions are drawn from the usual type of test.

The tall, thin, underweight subject is usually considered the type particularly liable to syncopal attacks. This is borne out in the present series, for 45 per cent of those in this section were more than 3 lb below their estimated normal weight. Only 21 per cent were of about normal build, the remaining 34 per cent being more than 3 lb above their estimated normal weight. In peace-time over 60 per cent of fit pilots were of about normal build (Treadgold, 1933). It thus appears that underweight and overweight men are more liable to syncopal attacks than men of average build.

Fainting due to cardiovascular causes may arise because of cerebral anaemia, cerebral congestion, or because of some alteration in blood chemistry.

Cerebral anaemia associated with haemorrhage. Five cases of fainting, all occurring on the ground, were due to this cause, in four instances as the result of bleeding from a peptic ulcer and in one instance from a ruptured spleen.

The airman who ruptured his spleen, a Wireless Operator Air Gunner, had before the haemorrhage been on anti-submarine patrol and felt quite well during the flight. When about an hour from base he extricated himself from the rear turret, a feat of some difficulty, necessitating forced hyper-extension of the spine. He walked to the wireless set and was sick without any preceding nausea. This was followed by severe abdominal pain, sufficient to double him up, but he managed to carry on as they were flying through cloud. When the machine landed the pain was better, but he fainted in the ambulance just as he reached hospital. At operation the abdomen was found to be full of blood and the splenic artery ruptured. When he had recovered, investigation showed increased fragility of the red cells, and a diagnosis of acholuric jaundice was made.

Cerebral anaemia associated with infection. In 25 cases the attack or attacks of syncope were associated with infection. Three cases had active pulmonary tuberculosis, three latent malaria, three tonsillitis, four upper respiratory tract infection, two sinusitis, and two an unexplained fever. The other infections were of various types and included one case of jaundice, one of kala-azar, and one of bacilluria. It is more than likely that in some of these patients the infection played only a small part in producing the attacks or may even have been simply coincidental. In most instances, however, it seemed to be the predominant factor.

Cerebral anaemia associated with heart disease Ten patients were found to have a heart lesion. In four instances there was a valvular defect of the heart—two patients had aortic regurgitation, one aortic stenosis and complained of dizziness only when doing violent aerobatics, and one had mitral stenosis. The remaining six had disorders of rhythm—three paroxysmal tachycardia, one paroxysmal auricular flutter accompanied by varying heart block, one atypical bundle branch block, and one very numerous extrasystoles. All patients except one were made permanently unfit for flying. The exception was the patient with paroxysmal flutter.

This was an Officer Air Gunner who had done over 400 hours flying, of which 300 were operational. He began to complain of momentary attacks of dizziness occurring as often as three times in an hour, but never while flying. On investigation he was found to have periods of auricular flutter with varying block, alternating with a regular rhythm or with occasional or repeated extrasystoles. The periods of irregularity ceased in May 1943, and after some months of freedom from attack he returned to operational flying and completed another tour of operations.

Cerebral anaemia associated with pain In seven patients the attacks were associated with bouts of pain, four occurring in the air and three on the ground. Two of the cases occurring in the air, both in pilots, were associated with severe pain in the ear while diving the machine, one patient had severe abdominal pain the result of distention of gas, and one a severe pain in the chest, thought to be due to a spontaneous pneumothorax, although no confirmatory evidence could be found when he was X-rayed a few days later.

Cerebral anaemia associated with hypotension The importance to be placed on a finding of hypotension has always been a matter for controversy, and moreover there is no general agreement as to the exact level at which hypotension may be said to begin. In the Royal Air Force the lowest normal blood-pressure levels are considered to be, systolic 110 millimetres of mercury, diastolic 70 millimetres of mercury. It cannot be too strongly emphasized that a single finding of hypotension according to the standards given above is comparatively frequent in young adults and probably far commoner than is generally imagined. The incidence of hypotension found at one examination among young adults of the 18 to 25 years age group, given by different observers, varies considerably, anything from 3 to 80 per cent having been reported as hypotensive. In the Royal Air Force, where a standard method of blood-pressure estimation is in force, the figure of 12.5 per cent has been given (Rook and Dawson, 1938) and is one with which the present series may best be compared. When repeated examinations of blood-pressure are made the numbers showing a persistent tendency to low pressure are comparatively few. In the same paper it was shown that in 584 pilots only nine, or 1.5 per cent, showed hypotension in 50 per cent or over of three or more examinations done at intervals of not less than a month. It is thus essential when considering this question to distinguish carefully between a

solitary finding of a slight degree of hypotension and one in which it is present in a majority of a number of examinations. It is only to these latter persons that the term hypotensive should apply. Young (1941), working with the United States Navy, has brought forward some figures concerning fatal accidents to candidates for naval cadetships which, if substantiated, would alter completely the importance to be attached to a low blood-pressure. He reported that of 159 fatal flying accidents nearly 50 per cent of the men involved manifested some form of hypotension. This has not been the experience in the Royal Air Force, for in an unselected series of 62 fatal flying accidents to pilots under training only eight (13 per cent) showed any degree of hypotension, a figure to be expected in a group of young men. The number of persistent hypotensives in all groups in the present series was 28, a percentage of 5.6, which is significantly higher than that found in the control group noted above, where only 1.5 per cent were persistently hypotensive. While hypotension is usually compatible with full health, there can be no doubt that it does indicate an increased liability to fainting attacks. Many instances of successful hypotensive pilots could be given, but the finding calls for great watchfulness and may well turn the scale when history or physical efficiency are not above criticism.

Cerebral anaemia associated with undue sensitivity to centrifugal force. Seven patients were reported to show an undue sensitivity to centrifugal force so that they 'blacked out' easily and lost consciousness. Ability to withstand this form of stress varies greatly among different individuals and seems to have no direct relation to the blood-pressure. Only one of the seven cases was a persistent hypotensive, showing hypotension in three out of five examinations done at different times. One patient with a normal blood-pressure, who was tested at Farnborough, 'blacked out' at 2G and was unconscious at 3G. Another who had had no trouble prior to an accident in which he ruptured his liver, subsequently developed considerable sensitivity, during a test he had a severe loss of consciousness at 5G. This patient's blood-pressure was taken on 12 occasions during a period of five years and gave a hypotensive reading on three occasions.

Cerebral anaemia associated with fatigue. Fatigue was given as the principal cause of an attack in 18 instances. Usually there was a history of lack of sleep either due to the urgency of operational flying or because of difficulties in travelling, often associated with long periods without food. Three patients showed persistent hypotension, one giving a hypotensive reading in seven out of 11 blood-pressure estimations. Four others had one low reading out of several that were done.

Cerebral anaemia associated with heat. In 15 cases the attack was thought to be due to hot, stuffy atmospheres, either an ill-ventilated room or compartment or in the tropics. One pilot set out early on a cold morning from England dressed in battle-dress which became unbearably hot when he reached the Mediterranean some hours later, others complained of the heat in the aircraft, usually in a shut-in navigational cabin.

Cerebral anaemia associated with cardiovascular inefficiency This rather indefinite group was considered to include 31 cases. Some of the difficulties in judging the degree of nervous tension in airmen have already been discussed and it is in this group that much trouble arises. The majority had fainted either as the result of standing on parade or while in church or gave a definite history of postural giddiness. In a few cases the attack followed slight injury. It is likely that emotion played a part in some of these patients, as it almost certainly did in others recorded in this section. It is felt, however, that the part it played had not the preponderant influence that it had in the cases regarded as primarily emotional in origin and grouped in the next section.

Cerebral congestion *Loss of consciousness associated with coughing* Four cases occurred in which consciousness was lost after attacks of violent coughing. One Flying Officer Pilot was sitting quietly drinking beer when he choked severely, eventually losing consciousness during which he was convulsed and passed urine. Another officer caught whooping-cough from his daughter and had a number of 'black-outs' associated with spasms of coughing. In one attack he lost consciousness completely and had convulsions. A third officer had coughing attacks as a result of asthma and chronic bronchitis and, on rare occasions, had lost consciousness completely, without however any convulsions being reported. These three patients all had an electroencephalogram done, which was reported as normal. These cases are similar to those classed as laryngeal epilepsy (Whitty, 1943), but it is felt that cerebral congestion was a more potent influence in causation than any latent epileptic tendency. The question is discussed in greater detail elsewhere (Rook, 1946). One further case of loss of consciousness associated with coughing occurred in an officer who was being examined in the decompression chamber. He had an attack of so-called 'chokes', a respiratory form of decompression sickness occurring at high altitudes and characterized by pain in the chest, cough, and shallow breathing. At the time he was at a simulated height of 36,000 feet. The causes of the symptoms are not completely understood. Some of the factors involved, apart from the cough, are the severe pain in the chest which may itself lead to collapse and some degree of anoxia due to spasm of the respiratory muscles in an attempt to ease the pain. It is difficult to know where to place this case, but in this group seems the most satisfactory.

Attacks associated with arterial hypertension Hypertension is a rare cause of fainting and dizziness among pilots and aircrew, for the routine blood-pressure estimations nearly always detect the condition before symptoms occur, and the patient is taken off flying. In two cases dizziness or loss of consciousness was associated with hypertension.

One Sergeant Air Gunner complained of headaches and dizziness, specially in coming out of a dive. His blood-pressure had been known for some time to be high for his age—systolic pressure 180 mm. of mercury, diastolic pressure 116 mm.—and he was taken off flying permanently.

An Officer Bomb Aimer, serving in Italy, had an attack of what was apparently hypertensive encephalopathy causing unconsciousness in the air. On admission to hospital he was still in coma and the blood-pressure was found to be 232/132, coming down on recovery to consciousness to 150/110. This case has already been reported by Ironside and Batchelor (1945). When seen in England he had recovered completely and the blood-pressure was 160/95. He returned eventually to limited flying duties for a period, then to full flying.

Alterations in blood chemistry Disturbances in cerebral oxygen supply Undue sensitivity to diminished oxygen tension was seen in two cases. Both were aircrew sergeants who had fainted while in the air at heights of about 15,000 feet. When tested in the decompression chamber both began to get symptoms at simulated heights which the normal subject could withstand easily. These symptoms always occurred at about the same level, whether or not they knew the simulated height at which the chamber was. In one of these two airmen tests done at the Royal Air Force Physiological Laboratory at Farnborough showed the blood-oxygen levels to be considerably lower than the normal at heights above 10,000 feet. In neither instance was there thought to be any marked emotional disturbance. In three further cases the symptoms were due to anoxia, the result of interference with the oxygen supply when at height on operational sorties. In one case the microphone froze and was rendered useless, while changing the helmet anoxic symptoms supervened. The second patient vomited so persistently on his first operational trip that his mask was off for too long a period and unconsciousness resulted. The third became panicky and, feeling suffocated, pulled his mask off. In the last two cases, although the actual symptoms resulted from anoxia, the basic cause was emotional and they might justifiably have been included in that category. The last case in this group was due to carbon-monoxide poisoning.

The patient was an Instructor and at the time was flying a light training machine, using the hood for practising blind flying, when he began to get symptoms. He had sufficient presence of mind to bale out and when landing suffered a fracture of the cervical spine without injury to the cord. On examination, immediately after landing, his blood was found to contain 50 per cent of carboxyhaemoglobin.

Hypoglycaemia Two cases occurred in the series which were thought to be associated with disordered sugar metabolism.

The first was a Sergeant Air Gunner of Coastal Command who had done over 500 hours flying of which 380 were operational. He began to complain of attacks of an empty feeling in the stomach, tremblings, palpitation, dizziness, and perspiration, symptoms which were relieved by eating and drinking. His morale was regarded as excellent both by the Medical and Executive branches. A blood-sugar curve after 50 gm of glucose showed a marked hypoglycaemia, while hourly blood-sugar readings done throughout the morning during a normal day showed levels of around 40 to 50 mg of sugar per 100 c.c. It was thought that the condition might be due to a pancreatic lesion, and Air Vice-Marshal Geoffrey Keynes performed a laparotomy, but

nothing abnormal was found. Subsequent to the operation, for some obscure reason, symptoms were less but the blood-sugar remained low. A blood-sugar done by Professor E C Dodds showed a fasting level of 83 mg per 100 cc and, at half-hourly intervals, levels of 120, 66, 62, and 55 mg per 100 cc. The patient was very keen to continue flying and was allowed to do so in view of the good reports obtained from his unit. He was warned about the importance of carrying food for himself, specially on long trips. He completed a further operational tour without trouble except for rather persistent air sickness.

The second case, which was far from definite and may well have had other causes, occurred in an Officer Pilot who had done 800 hours flying, 25 of which were operational. When examined originally he was noted to have glycosuria and was rejected. A few months later he was accepted on production of a certificate stating that the glycosuria was due to a low renal threshold and a lag curve. Three years later, while running up his engine for testing purposes and without any idea of taking off, he suddenly lost consciousness. At the time he was in the throes of considerable domestic worry, but had undergone no flying stress. For some time he had had a poor appetite and was eating little. He had taken no food for some hours prior to the attack, and he himself suggested that it was due to starvation. Several months later, after he had been returned to flying, he reported sick with loss of weight and sugar was again found in the urine. Investigation showed he was now diabetic and he was invalided from the Service after being stabilized on 14 units of insulin a day. It was thought that the attack might have been related in some way to the disorder of sugar metabolism.

Allergy The occurrence of loss of consciousness during attacks of allergy has been described (Wallis and Nicol, 1923), but is not a common condition. Dewar (1941) concluded that there was a relation between allergy and epilepsy, but it seems probable that the former is no more than a precipitating factor. The method by means of which allergy produces syncope is obscure. Two cases, both of a syncopal type, occurred in the present series, and others have been seen in ground personnel.

In the first case an Officer Pilot had complained for some months of attacks of angioneurotic oedema affecting chiefly the eyes, lips, and tongue. The attacks were nearly always preceded by abdominal upset with diarrhoea, and also seemed to be related to worry. During an attack of more than usual severity he fainted while going to the lavatory. Gradually the attacks of oedema began to pass off and he eventually returned to full flying duties.

The second patient, a Canadian Warrant Officer, had a number of attacks of fainting, all associated with an urticarial rash and sometimes swelling of the face. The rash could be produced by violent exercise and in some instances the attacks of fainting had been so provoked. He was made permanently unfit for flying.

Poisoning One patient, a Sergeant Air Gunner, drank an unstated quantity, but thought to be about a teaspoonful, of Sloan's liniment as a cure for a cold. Half an hour later he had a convulsive attack. This liniment contains 20 per cent of synthetic oil of camphor (Martindale, 1943), a drug which is well known as a convulsant. He was made permanently unfit for flying, a decision which seems open to criticism.

Cases Regarded as Primarily Emotional in Origin

Diagnosis The importance of emotion as a factor in the causation of loss of consciousness cannot be over-estimated. In war-time, overshadowing all other causes, disturbances of the higher levels of consciousness, particularly those due to fear, are the chief basis of attacks of loss of consciousness operating alone or through the lower cerebral levels. Some airmen on operational work are in a state of nervous tension which may persist throughout the whole day, so that a stimulus which would normally be ineffective may easily produce symptoms. 'Anxiety of mind occasioned by the symptoms themselves and the subsequent prostration when the storm is passed are apt to keep the patient in an unduly receptive state and so prone to further storms' (Ryle, 1934)

An Air Gunner who had done 250 hours flying of which 10 were operational, was involved in an accident as the result of overshooting the aerodrome. A few flights later, while flying straight and level in calm weather on a non-operational flight, he suddenly fainted for no apparent cause. Subsequent questioning elicited the fact that he had become extremely apprehensive in the air. On the flight in question he had felt physically fit but in a state of extreme nervous tension. A sudden change in the note given out by the engines, due to the pilot varying the pitch of the propellers, had sufficed to produce the attack.

When loss of consciousness occurs in anxiety states the cardiovascular system is usually at fault, but the attack may be due to hypersensitivity of the nerve-cells, for convulsive attacks, presumably epileptic, may occur only on operational flights, being absent during routine flying or when on the ground. It is difficult, if not impossible, to estimate accurately the fear state in others. Some do not feel afraid in a given situation, others may feel afraid but have sufficient control not to show it. Some are afraid of one hazard, such as flying over the sea, but will cheerfully accept another which does not involve this risk. Much of the education of the child to take his place in life is aimed at producing control over the emotions. In war-time restraint of fear often becomes of paramount importance in maintenance of morale in others, and so the presence of severe nervous tension may be concealed because it is the correct attitude to adopt. The great majority of cases of fainting in pilots and aircrew are due to emotional causes, but whether any given case should be classed as an example of an anxiety state or whether there is a hysterical factor of greater or lesser degree, seems of little practical importance. If the accepted definition of hysteria is that there should be included an element of motivation, albeit unconscious, so that gain results from the symptoms, is it likely often to be absent when flying casualties are occurring at the appalling rate that they did at one point during the war? Is the faint in some cases the counterpart of the trance-like state of the soldier who, unable to face his troubles, deserts his post? The airman cannot desert his aeroplane and must find another solution.

Diagnosis

Panic states
Emotion
Emotion after stress
Hyperventilation
Partially motivated

Total

TABLE IV
Cases Recorded as Primarily Emotional in Origin

Number of cases	Rank		Trade		Location of attacks			Disposal					
	Officers	Other ranks	Pilots	Aircrew	Under training	Air only	Ground only	Air and ground	Permanently unfit for flying	Full flying	Limited flying	Full aircrew duties	Temporarily unfit for flying
208	88	120	103	100	5	78	66	64	146	31	9	22	0
11	1	10	4	7	0	1	3	7	8	1	12	0	0
16	1	12	9	7	0	12	0	4	0	4	1	2	0
49	19	30	24	25	0	15	25	0	35	6	0	8	0
117	55	62	55	58	4	35	38	14	82	18	5	12	0
15	6	9	11	3	1	15	0	0	12	1	1	0	0

In some of the cases of 'black-outs' and faints the distinction between hysterical symptoms and actual malingering is very fine. Malingering is a serious diagnosis to have to make, but it is important while being fair to the patient to realize that others may become affected. Hence an apparently plausible story should not be accepted too readily. Sometimes some trivial upset, causing a mild attack of dizziness, renders the subject sensitive so that he is constantly expecting and imagining further attacks, sensory impressions of which previously he would have taken no notice are magnified, taking on terrifying proportions. The wide overlapping of the various factors causing loss of consciousness of psychological origin makes attempts at classification a matter of extreme difficulty. Fear and anxiety are the elements common to the section, and the various groupings represent different types of reaction thereto. Classification can be only loose, often unsatisfactory, and likely to portray the observer's personal bias.

Panic states Panic states occurred in 15 patients when, as the result of an acute fear reaction, an apparently fully conscious subject becomes completely unaware of the immediate purpose in hand and also to some extent of his environment. All attacks took place in the air, but four of the patients gave a history of syncopal attacks occurring on the ground prior to joining the Service. Some became unmanageable in the aircraft, struggling with other members of the crew, some got into a trance-like state resembling that described by Pavlov (1928), when extremely intensive external stimuli bring about a reflex inhibition of the motor region of the brain, similar to the condition of 'freezing' in animals, some carried out complicated actions such as firing a gun. One pilot, whenever he was faced with a difficulty in the air, got into a state in which his mind was a complete blank and for a period he could neither move nor think—how he managed to do 40 hours flying without killing himself is difficult to understand.

A Polish Pilot had done some 800 hours non-operational flying before being posted to an operational squadron. Soon after arriving at his new unit he had a slight collision in the air while practising formation flying. A few days later over France during a fighter sweep he again collided in the air with his leader. In a panic he turned east ignoring all radio calls, and was stopped only at the German frontier by his leader, who managed to attract his attention by rocking his machine and induced him to follow back to England.

Anxiety state The biggest group in the series, numbering 117 cases, is associated with anxiety and inability to stand up to the stress of flying. Rather over half of those affected had done some operational flying. In a number of instances more than one factor was at work in producing the attacks, fatigue and anxiety being the usual combination. The duration of the attacks was commonly momentary, but some were said to have lasted an hour or more. Some of the prolonged attacks were frankly hysterical in nature, while simulation may well have entered the picture in others. In nearly every instance several attacks were reported.

Some patients referred their symptoms to the stomach or other viscus, and associated the dizziness or loss of consciousness with the supposedly diseased organ. One airman with a cardiac neurosis referred his symptoms to the heart, another with fibrosis of one lung, about which he was anxious, had symptoms at height, although, when he was tested in the decompression chamber, his blood-oxygen saturation was shown to be normal for the height in question. Symptoms commenced in a number after experiencing 'blacking-out' during a tight turn, this had frightened them unduly so that symptoms recurred as the result of anticipatory anxiety during the gentlest turn.

Anxiety after stress In 40 instances the attacks of fainting were stated to be related to some severe stress—in 34 cases to a crash of some severity, and in the remainder to frightening experiences with anti-aircraft gunfire, enemy aircraft, or the like. At least 15 of these patients were regarded as predisposed to neurosis, and it is likely that the crash or unpleasant experience was the terminal factor in a commencing anxiety state.

Anxiety associated with hyperventilation Increased respiration rate, with or without actual hyperventilation, due to emotional causes is a condition which has long been known to occur in the hysterical type of patient. As a result of the experience gained in the recent war it has been surmised to be of frequent occurrence in pilots and aircrew engaged in operational flying. Exactly how frequent it is is unknown, for an increase in breathing to double the normal volume is scarcely observable (Henderson, 1938). The symptoms are due largely to alkalosis, although other factors are at work, specially when an oxygen mask is worn. The symptoms include giddiness, lightheadedness, and faintness. The importance placed on this factor by different observers varies from a belief that it forms the basis of many attacks of loss of consciousness of emotional origin to the concept recently enunciated by American workers that syncope due to peripheral circulatory collapse is not a normal component of the hyperventilation syndrome. As McCance (1932) has pointed out, individuals differ greatly in their susceptibility to the biochemical changes which occur, some get symptoms with so little overbreathing that it is hardly noticeable, in others symptoms occur only after nearly an hour of overbreathing. Hence, although evidence of hyperventilation can often be obtained from a patient or from witnesses, it by no means follows that this was the sole factor in causing the symptoms. Engel, Ferris, and Romano (1945) have pointed out that while hyperventilation may not of necessity produce syncope, it may provoke symptoms indirectly by means of at least five different mechanisms. The two most important of these are the production of syncope in anxious patients who are made more anxious still by the subjective symptoms due to the overbreathing, and the cumulative effect of overbreathing on an already unstable circulatory system. A history suggesting that hyperventilation had played a major part in the production of symptoms was obtained in 16 patients.

In one case, a Sergeant Air Gunner on his first operational sortie felt sleepy on reaching 20,000 feet and asked for more oxygen to be turned on,

after which he felt better. Soon after he saw flares and anti-aircraft shells bursting for the first time, he became dizzy and the pilot thought that he sounded as if he were drunk. It was then reported that he lost consciousness and, although he regained it momentarily on several occasions, he remembers nothing definite until the machine was over the English coast. On getting out of the aircraft he felt shaky and was white, but the Medical Officer found nothing on examination except that he was breathing rapidly. Ten hours later the hyperpnoea was still marked and it was noticeable on the following day. The attack was emotional in origin, but whether the increased breathing played a part in the production of the symptoms it is impossible to say.

Simulation The dividing-line between attacks due to emotion with a large hysterical element and frank malingering is very difficult to assess. In practice, although it may seem certain that symptoms are being simulated or grossly exaggerated, proof is almost impossible. Often the man is obviously of poor morale, and the impression gained from the history and the reports from his Commanding Officer and Medical Officer add confirmation of the nature of the attack. In some instances an original attack was probably genuine, but the account is exaggerated and subsequent attacks are simply imaginary. Most members of the Flying Branch know full well the seriousness with which attacks of unconsciousness are viewed by the Medical Department and realize that it is one of the easiest ways to escape flying duty. Some considerable degree of motivation was thought to have occurred in 11 cases, while it was almost certainly present in others, but as there was some doubt they have been placed in other groups. Only three of the 11 had done any operational flying and only one of these had put in more than 30 hours of operational work. In most of the cases the history was extremely vague and often inconsistent. Two patients when being examined attempted to falsify the results of medical tests, two others acknowledged having taken a violent dislike to flying. In two further cases the symptoms were probably being simulated to cover a gross error of judgment.

One of these, a pilot of some experience, after a short period in the air during a training flight, attempted to land without letting his undercarriage down on the wrong runway of a satellite aerodrome when he should have landed at his parent aerodrome. He said he felt hazy and dazed following a 'late night' and that he had inadvertently pulled the wrong lever. There were no objective symptoms of fatigue when he was examined after landing and he was apparently quite well. The electroencephalogram was normal. The Executive report was very bad and the crash was put down to laziness. He was seen five months later and in the interval had had no trouble physically. The Executive report was again bad. The symptoms were almost certainly simulated, in order to cover a crash due to his own stupidity.

Cases of Doubtful Origin

There is so much inter-relationship between the various factors associated with loss of consciousness that, even with the widest generalizations, individual cases will cause doubt. In 17 of the cases it was felt that the evidence

TABLE V
Electroencephalogram Results in Various Sections and Groups

Section	Group	Number of patients examined	++	+	Percent- age ++ and +	±	Changing	Normal	Percent- age normal	Not ex- amined
Total neurogenic section	—	103	31	14	46	10	5	43	42	18
	Major idiopathic epilepsy	49	17	9	53	6	2	15	31	4
	Doubtful major idiopathic epilepsy	1	3	0	75	0	0	1	25	2
	Minor idiopathic epilepsy	8	2	1	38	1	0	4	50	2
	All epilepsy cases	61	22	10	53	7	2	20	33	8
	Single convulsive attacks	19	6	3	47	0	1	9	17	1
	Loss of consciousness after injury	13	0	1	8	2	2	8	61	0
	Cerebral necroplasm	5	3	0	60	0	0	2	40	0
Total cardiovascular section	—	94	9	6	17	10	3	66	71	60
Total emotional section	—	89	6	6	13	10	2	65	70	110
Doubtful cases	—	13	2	0	15	1	1	9	69	4
All cases	—	209	48	26	24	31	11	183	62	201

was so doubtful that no diagnosis could be made. It is probable that most of these cases belonged to the emotional group, but there was often considerable difference in the opinions expressed.

One Officer Air Gunner complained that for a number of years he had had attacks of 'a far away feeling' in which he felt confused for several minutes. He had not disclosed these symptoms on entry into the Service. His unit Medical Officer thought that he was a malingerer, one neuro-psychiatrist favoured epilepsy, a second early Mènière's disease. The otorhino-laryngological specialist disagreed with the last opinion. The patient was an anxious worrying type who had developed a mild anxiety state after his first tour of operations and his symptoms were probably emotional.

The electroencephalogram The exact value of the electroencephalogram in cases of the type under discussion has not yet been completely determined. Until more evidence is available the correct attitude for the clinician has been indicated by Gibbs (1943), 'The electroencephalogram is now entering its statistical phase when large series of normals require investigation. A positive or negative electroencephalogram is only suggestive but it may be highly suggestive'. A note of warning on a too liberal interpretation of the value of the electroencephalogram has also been sounded by Williams (1944). One fact alone is enough to disconcert the clinician, namely, the number of occasions when records taken at intervals of a few months show marked changes in the results. There can be no doubt that the tendency of some observers to make the diagnosis of epilepsy too embracing is both unscientific and unfair to the patient. Epilepsy, at any rate so far as the Service is concerned, is a diagnosis that should be made with the same circumspection as a diagnosis of pulmonary tuberculosis. In both there are social implications and a high degree of certainty is necessary before the label is applied. It is essential therefore that too much weight should not be put on a positive electroencephalogram when the clinical evidence does not point the same way. An electroencephalogram was done in 299 of the 500 cases and the results are tabulated in Table V. The reports have been classified under four headings:

++ when the report indicated the presence of larval attacks or was strongly suspicious of epilepsy

+ when the report stated that the record pointed to an epileptic basis for the attack

± when the report recorded an abnormality, but one that was not suggestive of epilepsy, and

Normal

Changes in the electroencephalogram results, when the examination was repeated after a period usually of a few months, occurred in 11 cases. In five instances the first electroencephalogram was reported as showing evidence of an epileptic basis for the attack, while a second was reported as normal. In two instances a positive record was obtained at the first examination while at a second examination the record, while abnormal, did not

suggest epilepsy as a basis for the attack. In one instance an abnormal record which did not suggest epilepsy was obtained at the first examination, but at a second examination a normal record was obtained. In two cases the first record was normal while a second record pointed to epilepsy, in one case a first record was normal while a second record was abnormal but did not point to epilepsy.

Comment

Certain important practical points emerge from the analysis of the cases studied here which shows that in war-time this type of case is a serious source of wastage, for 325 of the 500 cases (65 per cent) had to be permanently removed from flying duties.

History Even allowing for mistakes, it is obvious that the relevant history obtained from candidates on joining the Service is often valueless. The inaccuracy of the history given by the candidate himself is due to at least two reasons—a desire to suppress facts which he feels may adversely affect the decision of the Board and a lack of knowledge or understanding of some of the occurrences of his past life and family history. The fact that a relative is in a mental hospital or is an epileptic is often hidden from the children of a family. Similarly the importance of attacks of fainting in early life may easily have been minimized so that such incidents really have been forgotten. A partial solution would be for a near relative, preferably the father or mother, to accompany each candidate when he appears for selection, as has been suggested by Symonds (1945). A relative is more likely to be able to give, and also to be willing to give, a proper history. The history, the most important single factor in the examination, is often inadequately taken. Besides giving information that can be obtained in no other way, it gives an insight into the psychological make-up of the candidate which can be of the greatest importance. There should be sufficient medical staff and the examination arrangements should be so organized that there is adequate time to investigate fully any clue which might lead to some important finding. It is useless to spend much time on psychological and other tests of doubtful value when time to take a proper history is lacking.

Routine electroencephalogram The advisability of doing a routine electroencephalogram on all candidates for flying duties has been suggested, but is considered to be of doubtful value (Williams, 1945). It would, however, seem worth while in any candidate giving a history of one or more fainting attacks. The combination of such a history and an abnormal electroencephalogram weighs so heavily against a candidate that everything possible should be done to eliminate these individuals before training commences.

Disposal There can be little argument about the disposal of pilots or aircrew who have had two or more recent attacks of loss of consciousness. Immediate prohibition from flying is the only course, either permanently or at least for many months, unless the cause is known and is removable. It

matters not at all whether the attacks are neurogenic, syncopal, or emotional in nature, they are equally dangerous in the air. The chief difficulty arises when a single attack has occurred or when, after several months or years of freedom from any tendency to fainting, there is a single recurrence. Usually, when epilepsy is not in question, no harm can come from delaying the decision for a few months if the patient is taken off flying duties and watched carefully in the interval. The question is often posed, would you like to fly as a passenger with a pilot who has had a single attack of loss of consciousness of doubtful origin? Obviously if the comparison is with the pilot of similar experience and carefulness, there can be no doubt as to the choice, but if the patient in question has had only one attack, if he has been watched for six months or more without any sign of recurrence, and if he is a good and careful pilot with many flying hours to his credit, it might well be safer than flying with a less-experienced pilot.

Summary

1 Five hundred consecutive cases of impairment of consciousness among pilots and aircrew have been classified into three groups, neurogenic, cardiovascular, and emotional.

2 The three groups are ill defined and merge into one another, so that it is often difficult to say which is the predominant factor in any given patient. In 17 instances there was so much doubt that classification was impossible.

3 The neurogenic group comprised just under a quarter of the total, about half of them cases of epilepsy. The influence of fear as a causative factor of epileptic attacks seemed to be of more importance than is commonly supposed.

4 The cardiovascular group comprised rather over a quarter of the total. It was made up of a number of small groups in which cardiovascular inefficiency was the main element, either acting alone or in association with infection, fatigue, or with poor reaction to raised temperatures.

5 The importance of hypotension in relation to aviation medicine is discussed. While considered to be no certain bar to flying duties it is an indication for caution.

6 Rather under half of the cases were classified as emotional in origin, ranging on the one hand from the acute panic states to hysteria and simulation on the other.

7 An electroencephalogram was done on 299 of the patients. In the neurogenic group nearly 50 per cent of the electroencephalograms pointed to an epileptic basis for the attack, in the other groups 15 per cent were positive. A change in the electroencephalogram when repeated occurred in 11 instances.

8 The importance of obtaining a full history in all candidates for flying duties is stressed.

9 Hasty decision in recommending withdrawal from flying duties is to be deprecated. In many instances a period of observation in a 'ground

category' does no harm, may assist in arriving at a definite diagnosis, and may eventually allow a return to flying

The greater part of the work on which this analysis has been based was done by the officers who worked at the Central Medical Establishment during the latter part of the war and to all of these I am deeply grateful. In particular I should like to thank Air Commodore H L Burton with whom I have discussed the subject many times both before and during the war, Wing Commanders N S Alcock and K Latter for special help from the neuropsychiatric point of view, Wing Commander D Williams for helpful criticism and for assistance over the electroencephalographic side of the analysis, and Squadron Leader W K Stewart of the Royal Air Force Physiological laboratory for help with decompression and 'black-out' tests. I should like also to thank the airmen and airwomen of the office staff, especially Warrant Officer J A Patchett, Sergeant J R Dean, Corporal G G James, and Corporal J S Young who have done so much to ensure that no cases should be missed and that medical records and documents should always be available for study.

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AN OUTBREAK OF SEVERE INFECTIVE HEPATITIS IN BURMA¹

By J F STOKES AND A A MILLER

With Plates 5 to 10

ONE of the few redeeming features of a war is that it provides an opportunity for the study of some diseases less frequently encountered under conditions of peace. The fact that the exploitation of this opportunity to the full is so often hampered by the hurry of operational service has not prevented considerable additions being made to our knowledge of various diseases, including infective hepatitis. This malady has long been recognized as essentially a military disease, the *Soldatenkrankheit* of the Germans, the *jaunisse de champs* of the French (Lucke, 1944). The new knowledge gained in respect of infective hepatitis in the 1939-45 War has fallen largely under three heads—a greater understanding of its epidemiology, the sure recognition of homologous serum hepatitis as a closely allied if not identical condition, and the better appreciation of the pathological processes at work in the terminal stages of the disease. Lucké's (1944) admirable analysis from the pathological standpoint of 125 fatalities has provided the greatest advance in the last direction. Experience of 64 fatal cases of infective hepatitis in South East Asia between 1944 and 1946, over half of which occurred in a sharp outbreak centred on Rangoon, leads to a broader conception of the clinical pictures which may be produced and contributes further to the clarification of the pathological processes involved, particularly in short-lived cases, which are but rarely observed.

Hepatic necrosis is well known as an occasional complication of infective hepatitis, but its occurrence has not often been sufficiently frequent to demand a great deal of attention (Cockayne, 1912, Wilson and Goodpasture, 1927, Bergstrand, 1930, Cullinan, 1939, Wang, 1945). In the American Civil War 231 fatalities in 52,429 cases were observed, and the mortality rate amongst British and Indian troops in Mesopotamia during 1914-18 was 0.4 per cent (Hurst, Barber, Knott, and Ross, 1941). The German Navy showed a death-rate of 0.13 per cent between 1919 and 1929 (Lucké, 1944), and Bergstrand (1930) reported 95 deaths in the Scandinavian epidemic. Mortality in Finland was recorded by Wallgren (1930) as 0.34 per cent, and in Sweden by Selander (1939) as 0.2 to 0.4 per cent. In the recent war, Cameron (1943) has reported no deaths in 250 cases in Palestine, Gordon (1943) no deaths in 168 cases in the Middle East Forces, and van Rooyen and Gordon (1942), from the Mediterranean Expeditionary Force, concluded

¹ Received March 24, 1947

that, despite its high morbidity, the mortality rate from infective hepatitis was negligible Findlay, Martin, and Mitchell (1944), however, reported a death-rate of 0.2 per cent from West Africa, and Luckó (1944) has studied 125 deaths in the American outbreak, these were from a very large series and represent a mortality rate of 0.24 per cent. The overall death-rate in the Central Mediterranean Forces is estimated at 0.2 per cent. On the other hand, rates of 2.4 per cent in Brazilian natives (Fox, Manso, Penna, and Pará, 1942) and 3.0 per cent in Africans (Oram, 1945) have been observed, these have in each instance been correlated with dietary deficiency.

No detailed figures are available for death-rates in the Far East, but experience in the four main hospital centres in Assam and Bengal suggests that it was approximately 0.15 per cent in 1944-5. In South Burma from July 1945 to January 1946 the mortality rate was 2.0 per cent, though there was only one fatal case (0.16 per cent) in North Burma over the corresponding months. It may be pointed out that South Burma differs from North Burma not only in its administrative control, but also in its climate which is hotter and more humid. The dividing line between the two areas is something more than an arbitrary military boundary.

Many reports of outbreaks of infective hepatitis have appeared as a result of the War of 1939-45 (van Rooyen and Gordon, 1942, Cameron, 1943, Gordon, 1943, Havens, 1944, Spooner, 1943, Jayawardene, 1945, McFarlan, 1945). The addition of another would be without value were it not for the fact that it records two unusual features, firstly a higher mortality rate than is usually recorded, and secondly a high proportion of deaths in the early stages of the disease.

The Outbreak in Burma

There were 24 fatalities in 1,200 cases of infective hepatitis in South Burma between 1 July 1945 and 31 January 1946. These have been analysed statistically. Ten more occurred between 1 February and 30 June 1946. Of these 34 cases, 23 have been personally observed and 11 have been assessed on autopsy specimens, consideration of their records, and discussion with those under whose care they died. During this period four other cases of infective hepatitis were in coma for over 48 hours, but ultimately recovered. The distribution of deaths by months is shown in Fig. 1.

Geographical distribution In deciding the place at which the disease was contracted it is necessary to know not only the man's previous movements, but also whether there was any possibility of his jaundice being due to homologous serum hepatitis rather than epidemic hepatitis, since the incubation period for the former is longer. While it is realized that a history of having had an injection of arsenic or penicillin or an infusion of blood or plasma does not necessarily imply that subsequent jaundice is due to homologous serum hepatitis, all patients in whom there was a history of injections were allowed an incubation period of up to five months. Those patients who were unquestionably suffering from epidemic hepatitis were allowed an

incubation period of up to six weeks Twenty-two out of 34 cases (65 per cent) apparently contracted the disease in Rangoon

Racial incidence Of the 34 fatal cases, seven were British, 17 Indian, nine African, and one Japanese Apart from one British officer all these were other ranks

Population at risk The troop strengths in Burma between July 1945 and January 1946 are shown in Table I That the case mortality had risen to

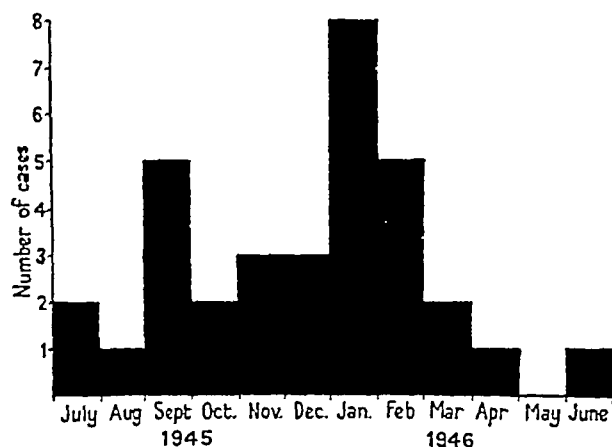


FIG 1 Monthly occurrence of onset of disease in fatal cases of infective hepatitis in South Burma

TABLE I

Troop Strengths in North and South Burma

	South Burma	North Burma	All Burma
July, 1945	172,500	67,100	239,600
August	214,500	64,500	279,000
September	193,300	62,300	255,600
October	157,900	63,700	221,600
November	151,300	68,700	220,000
December	147,100	55,900	203,000
January, 1946	144,800	61,800	206,600

a statistically significant extent from July 1945 to January 1946 is shown by the following data

	July	Aug	Sept	Oct	Nov	Dec	Jan	Total
Cases in South Burma	327	266	141	160	121	99	86	1,200
Deaths	2	1	5	2	3	3	8	24
Expected deaths	6.54	5.32	2.82	3.20	2.42	1.98	1.72	24.00

Grouping these figures to have at least five deaths in each cell, shows—

	July	Aug	Sept-Oct	Nov-Dec	Jan	Total
Deaths	2	1	7	14		24
Expected deaths	6.54	5.32	6.02	6.12		24.00

For this table, χ^2 is 16.966 and with three degrees of freedom P is less than 0.01 Thus the probability that the rise in death-rate could have occurred by chance is less than 1 in 100

If comparisons are to be made with other recorded death-rates, the highest mortality in any way analogous is that of 0.4 per cent in mixed British and Indian troops in Mesopotamia during 1914-18 (Hurst, Barber, Knott, and Ross, 1941). The proportion of Indian to British troops in the latter epidemic was approximately 1.5 to 1, and in Burma about 2 to 1. The mortality rate in Burma was 2.0 per cent. The standard error of the difference between the proportions of 2.0 and 0.4 is 0.42. The actual difference is 1.6, which, being

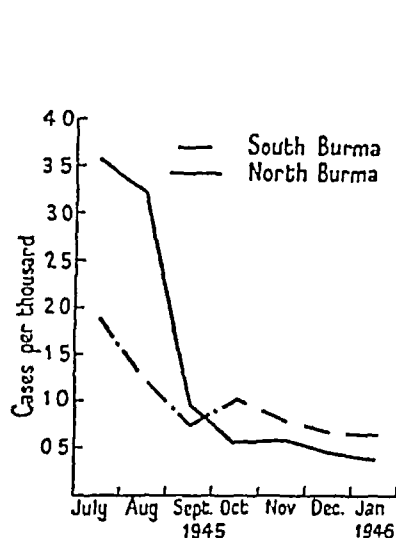


FIG 2 Monthly incidence of infective hepatitis in North and South Burma

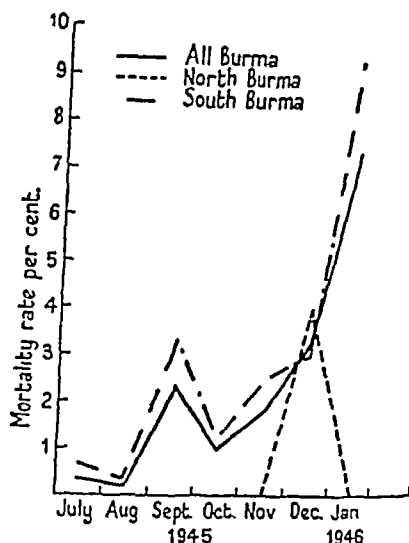


FIG 3 Monthly mortality rate from infective hepatitis in Burma

nearly four times the standard error, is significant. It will be seen that while there was a steady diminution in numbers of troops both in North and South Burma, there was no massive southward movement of troops which might have accounted for the number of fatal cases observed in South Burma. Though detailed figures for February to June 1946 are not to hand, the total number of troops continued to fall slowly.

Incidence of infective hepatitis in population at risk. The rates per 1,000 in North and South Burma are shown in Fig 2. It is seen that the incidence of infective hepatitis fell steadily in both areas, a little faster in the North than in the South. The autumn rise and winter peak, which might have been expected from experience of other epidemics, did not occur.

Mortality rates. The monthly mortality rates in North and South Burma are shown in Fig 3.

Clinical Features

The most striking feature of the outbreak was the swift clinical course pursued by many of the cases. In Lucké's (1944) series there were no patients who died within 10 days of the onset of symptoms, and he stated

'So far as I have been able to learn from the literature, no one has ever seen the earliest stages of this disease, which rarely terminates in its most acute stages' A War Office Medical Department Bulletin (1942) stated that death is rare in the first two or three weeks of the disease, and this has been the general experience, though Wood (1946) recorded eight cases dying within

TABLE II
Duration of Disease in Fatal Infective Hepatitis in Burma

Less than 10 days	7 cases
10 to 19 "	14 "
20 " 29 "	3 "
30 " 39 "	1 case
40 " 49 "	2 cases
50 " 59 "	0 case
60 " 69 "	0 "
70 " 79 "	1 "
80 " 89 "	1 "
90 " 99 "	1 "
100 " 109 "	0 "
110 " 119 "	1 "
Indeterminate	3 cases
Total	34 "

TABLE III
Duration of Pre-Icteric, Intermediate, and Final Phases in Fatal Infective Hepatitis in Burma

Pre-icteric phase		Intermediate phase		Final phase	
0 to 4 days	15 cases	0 to 4 days	14 cases	0 to 1 day	5 cases
5 " 9 "	7 "	5 " 9 "	6 "	1 " 2 days	14 "
10 " 14 "	6 "	10 " 14 "	2 "	2 " 3 "	9 "
15 " 19 "	2 "	15 " 19 "	3 "	3 " 4 "	4 "
Over 19 "	1 case	20 " 24 "	0 case	Over 4 "	2 "
Indeterminate	3 cases	25 " 29 "	1 "		
		30 " 34 "	0 "		
		35 " 39 "	1 "		
		Over 39 "	4 cases		
		Indeterminate	3 "		
Total	34 "	Total	34 "	Total	34 "

10 days, these were probably examples of homologous serum hepatitis, which often carries a worse prognosis than epidemic hepatitis

The total duration of the disease in the present series is shown in Table II. The three cases of indeterminate duration consisted of one man whose presenting symptom was coma and from whom no history could be obtained and two longstanding cases of doubtful duration. Of these fatal cases 20.6 per cent died in the first 10 days of the disease, and 61.8 per cent within the first 19 days. It is of interest to note the lengths of the pre-icteric, intermediate, and final phases. The pre-icteric phase is the period from the first onset of symptoms to the development of jaundice, the final phase from the occurrence of the first clinical suspicion of a fatal outcome (as will be seen later, this does not necessarily imply the onset of coma) to

death, and the intermediate phase from the end of the pre-icteric phase to the beginning of the final phase (Table III). These arbitrary subdivisions have been used by Lucké (1944) and they are recorded here to enable easy comparison with his series. Our figures emphasize two points. Firstly, there was a short intermediate phase in many cases. On seven occasions clinical jaundice did not occur till the onset of the final phase or shortly afterwards. If the final phase began at night and was complete before daylight, jaundice was first visible on the autopsy table. Secondly, there was usually a short final phase, to which attention has already been called (Stokes, Owen, and Holmes, 1945). In the five cases with a final phase of less than one day, the duration was 2, 4, 15, 20, and 22 hours.

Symptomatology Jaundice Jaundice was often absent in the short-lived patients until a few hours before death, and was absent throughout in two cases. The longer-lived patients were invariably deeply jaundiced.

Abdominal distension This was sometimes considerable in the longer-lived cases and was not always entirely due to ascites, for it could be partially relieved by enemata and the passage of a flatus tube. The gaseous fraction of the distension could be correlated with the presence of phlegmonous inflammation of the gut.

The liver The liver was palpable in the pre-icteric phase in eight of 34 cases, in the intermediate phase in 19 of 34, and in the final phase in two of 34. This is less often than was found in Lucké's (1944) series and is a reflection of the higher proportion of cases running a short course. The two cases in which the liver was palpable in the final phase were both of long duration, and attempted regeneration of hepatic tissue was a marked feature at autopsy. The liver was, as a rule, not to be felt in the final phase and the liver dullness receded and sometimes disappeared very quickly. Attempts to forecast the size of the liver from the extent of liver dullness usually failed. This was thought to be due to the reduction in dullness being the result of a falling away of the liver from the abdominal wall as much as an absolute shrinkage in size. Prigosen and Gordon's (1942) contention that a diminution in size of the liver may be the first sign of the onset of acute hepatic necrosis was not supported by the present series, in the absence of other signs it is as likely to presage recovery as deterioration.

Ascites Ascites was clinically demonstrable in eight of 34 cases. It was usually gross, had the characters of a transudate, and was always associated with those who lived longest.

Case 2 Pioneer B S, Indian, aged 34 years, developed anorexia, abdominal pain and vomiting on 1 July 1945 and became jaundiced on 6 July. Liver and spleen were palpable. On 14 July he complained of much flatulence which was relieved by an enema. Ascites appeared on 17 July. He had severe hiccup on the evening of 22 July, became restless and a little confused during the night, went into coma, and died the following morning. Serum-proteins were 4.45 gm per 100 cc.

Autopsy Ten pints of clear bile-stained ascites. A small nodular liver, deeply bile-stained, whose histology showed regenerative nodules and proli-

ferating bile ducts with no normal liver tissue. There was phlegmonous inflammation of the first part of the duodenum, terminal six inches of ileum, ascending colon, hepatic flexure, and four inches of descending colon. There were subpericardial and subperitoneal haemorrhages. The pancreas was harder than normal and showed acute inflammatory changes on section.

Oedema Oedema was observed in six of 34 cases. Five of these cases were among those who showed ascites. Oedema was present in the lower limbs in all six cases, but occurred in the upper limbs as well in three.

Case 6 Pioneer R C, Indian, aged 40 years, developed anorexia with fever on 7 September 1945, later became jaundiced, and had a liver palpable two fingersbreadth below the costal margin. He recovered his appetite, but the liver remained palpable and his jaundice did not completely clear. Jaundice began to deepen on 24 October, the liver became smaller and was not palpable on 4 November. The abdomen became distended on 13 November and ascites was present, there was also oedema of both ankles. On 16 November he was drowsy and incontinent of urine, ascites was considerable. He was comatose on 19 November and oedema was present in both forearms and hands. He died early on 21 November.

Autopsy Three pints of clear bile-stained ascites. Liver weighed 1,100 gm and showed changes of subacute necrosis.

Temperature The temperature was raised in 18 of 34 cases in the pre-icteric phase up to a maximum of 101° F, in four of 32 in the intermediate phase to between 99° and 100° F, and in 12 of 32 in the final phase up to a maximum of 107° F. The temperature in the intermediate phase represented a delayed fall from the pre-icteric phase. Once the initial fever had subsided, the temperature did not rise until the terminal hyperpyrexia.

Haemorrhagic signs Six patients had haematemesis, three bled from the gums, two had petechiae and purpura of the skin, one had subconjunctival haemorrhages, one bled into the ascites, and one presented with a severe epistaxis.

Case 8 Leading Aircraftman P, British, aged 23 years, had a severe epistaxis which demanded transfusion on 22 October 1945. After recovery from this he admitted to anorexia and abdominal pain for three months. The liver was easily palpable four fingersbreadth below the costal margin. There was slight jaundice on 16 November, a recurrence of epistaxis on 23 November, and bleeding from the gums on 1 December. The bleeding was not controlled by parenteral vitamin K or blood transfusion, and every injection was followed by a large ecchymosis. There was transitory oedema of the ankles. At this stage serum-bilirubin was 4 mg per 100 c.c. He began to go downhill on 11 December. Jaundice deepened (serum-bilirubin 15 mg per 100 c.c.), the liver became smaller, ascites developed (serum-proteins 5.1 gm per 100 c.c.), and on the same evening he became stuporose and passed into muttering delirium. He died early on 12 December.

Autopsy A small liver showing great loss of parenchyma, massive bile-duct proliferation and isolated groups of regenerating liver cells. There were subpericardial, subendocardial, pulmonary, subserous jejunal, and subcapsular renal haemorrhages.

Nervous signs These were confined to the final phase and occurred in every case in the series. The final phase was ushered in by the occurrence

of nervous or psychological changes varying from minor behaviour changes to the dramatic onset of coma within the space of a few minutes. A minimal change in behaviour might precede the onset of coma by as long as 24 hours, particularly in the longer-lived cases. In one case the behaviour change was so pronounced that, in the believed absence of any signs of organic disease, he was admitted to the psychiatric ward of a hospital.

The frequency of the first sign of deterioration is shown in Table IV. Coma ensued in every case. Eight patients showed violent delirium during

TABLE IV

Signs of Onset of Final Phase in Fatal Infective Hepatitis

Drowsiness	11 cases
Coma	8 "
Excited behaviour	6 "
Restlessness	3 "
Confusion	2 "
Listlessness	1 case
Insomnia	1 "
Repetitive movements of limbs	1 "
'Wandering aimlessly'	1 "
Total	34 cases

the early stages of coma, and six had spasticity of the limbs, more commonly in the lower than the upper extremities and affecting the large rather than the small muscles (these characteristics of the alteration in tone are the same as those observed in fatal cases in Assam and Bengal). Involuntary movements were present in six cases, they were jerky and choreiform in type, affecting the arms and legs in five cases and the head in two. Tendon reflexes were always brisk and sustained ankle clonus was present in eight cases. Extensor plantar responses were present in six cases, not necessarily those who showed other pyramidal signs. In addition, facial palsy, external rectus palsy, hemiplegia, and external strabismus were seen in single cases. These signs are in line with those previously recorded (Turner, Snively, Grossman, Buchanan, and Foster, 1944, Stokes, Owen, and Holmes, 1945).

Case 1 Leading Aircraftman F, British, aged 27 years, had had syphilis treated by penicillin in July 1945 and developed anorexia, abdominal pain, and vomiting on 6 August. He was jaundiced on 7 August and the liver became palpable on 10 August. He made normal progress till he became drowsy on 12 August at mid-day. He was confused the same evening, and the following day was violently delirious and semi-comatose. There was spastic paralysis of left face, arm, and leg, and a left external rectus weakness. Cerebrospinal fluid was normal in all respects. Urine contained a trace of albumen. He died on the same day.

Autopsy A flabby shrunken liver weighing 1,020 gm, showing extensive histological necrosis with no bile-duct proliferation and no regeneration. The kidneys were heavily bile-stained and showed mild tubular degeneration. There were subpleural, subpericardial, and extensive submesenteric haemorrhages, and submucous haemorrhages in stomach and small intestine. The brain was normal.

A fortnight after death a contact, who had been living in the same tent

for three months, developed infective hepatitis from which he made a good recovery

Laboratory investigations These were necessarily incomplete on account of the exigencies of field service and the pressure of routine work. The urine contained traces of albumen in six of 34 cases. White-cell counts ranged from 3,900 to 16,600 per c mm, and a normal or slightly leucopenic count was the rule. Serum-proteins ranged from 4.4 to 7.6 gm per 100 cc. No correlation was observed between the serum-protein level and the occurrence of oedema or ascites, but facilities were not available for performing differential estimation of albumen and globulin. Lumbar puncture always revealed a normal cerebrospinal fluid under normal pressure, the fluid was never jaundiced.

Clinical types Two clinical types, an acute and a subacute, were recognizable and are worth distinguishing, though it must be realized that the distinction is purely clinical, and the pathological changes observed in the two types, while differing in some respects, are all part of one continuous process. The acute type presented as coma of unexplained origin. The diagnosis was not always easy to make and it was apt to be mistaken for cerebral malaria, despite the rarity of the latter disease after the institution of suppressive mepacrine and the use of DDT. The patient might be admitted in coma or might suddenly go into coma a day or so after admission to hospital on account of vague malaise, fever, and anorexia. Jaundice would be either absent or slight. There might be a progressive rise in temperature. The pulse volume was usually good at first, in contrast to the shock that is so often found in cerebral malaria. The diagnostic physical signs were to be found chiefly in the abdomen and central nervous system. The liver, which might have been palpable and tender previously, as it may be in malaria, could no longer be felt, the liver dullness decreasing and disappearing at a remarkable rate. The pupils were dilated and there was incontinence of urine. Tendon reflexes were increased and ankle clonus often appeared before the end. Spasticity might occur. Plantar responses were usually flexor, but might be extensor. Involuntary movements of a choreiform type might occur, but were not common. Petechiae and purpura of the skin might be observed, though they are difficult to see in dark-skinned patients, but were surprisingly rare considering the frequency of gross haemorrhagic phenomena at autopsy. It might be difficult to staunch the flow of blood from a venepuncture. Death as a rule ensued within 48 hours of the onset of the final phase.

Case 15 Lascar S. D., Indian, aged 25 years complained of fever, anorexia, and constipation on 23 December 1945. On admission to hospital on 26 December the spleen was palpable, but not the liver. There was no jaundice. There were no malarial parasites in repeated blood-smears. The temperature subsided on 28 December, but on the same day he started to wander aimlessly round the ward and was confused. On 29 December he went into coma, jaundice developed, and he died in a few hours.

Autopsy A normal-sized liver with smooth capsule and purple and yellow mottling all over the surface. The cut surface was deep red with purple and yellow mottling. Sections showed extensive necrosis with massive haemorrhages into the liver and congested sinusoids. There was widespread infiltration with exudative cells and no attempt at repair. There were petechial haemorrhages into the wall of the left ventricle.

Case 19 Sepov G, Indian, aged 30 years, had anorexia and fever for two days before admission to hospital on 20 January 1946. There was a very faint tinge of icterus. The liver was not palpable, though normal liver dullness was present. He went rapidly into coma the same evening, had spastic limbs, sustained ankle clonus, incontinence, and dilated pupils. Cerebrospinal fluid was normal. He died four hours later.

Autopsy A small liver weighing 1,200 gm with a smooth surface and a reddish-yellow and purple colour. Cut surface was mottled red and yellow. Sections showed that most of the liver cells were destroyed. There were massive haemorrhages throughout the liver, engorged sinusoids, and numerous exudative cells, with no attempt at repair.

Case 16 Driver A N, Indian, aged 22 years, had anorexia, abdominal pain, and fever on 7 January 1946. On admission to hospital on 11 January there were no abnormal signs. He became jaundiced on 13 January. On 14 January he went into coma and showed bilateral sustained ankle clonus. Gums were bleeding and liver dullness was absent. Serum-bilirubin was 4 mg per 100 c.c. He developed generalized jerky movements of the body and died the same night.

Autopsy A small, dark red liver with a smooth capsule. The cut surface revealed intense congestion and a nutmeg appearance. Sections showed intense congestion of the sinusoids, haemorrhages, exudative cells, widespread necrosis, and no attempt at repair. There were extensive haemorrhages over the surface of both lungs and throughout the substance of both lower lobes. There were also subpericardial and subperitoneal petechiae and small haemorrhages in the lesser calyces of the renal pelves.

The subacute type pursued a less swift course and was characterized by the additional sign of ascites. There was a clear history of an attack of infective hepatitis which in no way differed from an ordinary attack. In some cases the patient was discharged from hospital with an apparent clinical cure, only to be readmitted later. Anything from two to 12 weeks after the onset ascites developed. At the same time there might be much gaseous distension of the abdomen, and the combination of these two factors caused the patient considerable distress. In one case repeated tapping was necessary to achieve symptomatic relief. Jaundice in the subacute case was always deep. The picture remained unchanged for about a week until it was interrupted by coma and a final phase which precisely resembled that seen in the acute case except in one respect, that of time relations. Some clinical warning was usually given by minor behaviour changes, and coma might last for three days or more before death ensued. During these three days the depth of coma might vary considerably as though a fine balance had been struck between the destructive and reconstructive processes.

operating concurrently in the liver, and one patient actually came out of coma for a few hours in the middle of his final phase

Case 18 L/Naik N S, Indian, aged 28 years, was treated for syphilis with penicillin in August 1945. He developed what appeared to be a quite ordinary attack of infective hepatitis for which he was treated in hospital from 9 November to 21 December with apparent cure. He was readmitted on 1 January 1946 with dyspnoea, constipation, and heaviness of the abdomen. He was deeply jaundiced (serum-bilirubin 8 mg per 100 c.c.) and had gross ascites and gaseous distension of the abdomen. Serum-proteins were 6.6 gm per 100 c.c. Serum-bilirubin was 14 mg per 100 c.c. on 19 January when he went into coma with spasticity of both upper limbs and very brisk ankle reflexes. He came out of coma for a few hours on 20 January and took a meal, but in the evening became comatose again, the temperature rose steadily and there was sustained ankle clonus. On 21 January the pupils were dilated, he was incontinent, and the signs remained unchanged till his death the following day.

Autopsy A small liver weighing 950 gm with increased fibrous stroma. The substance was greenish-yellow and studded with small round yellow nodules. Sections showed large regenerating areas and much bile-duct proliferation. There was gross ascites. The walls of the transverse colon were greatly thickened and the mucous membrane bulged in folds of gelatinous oedema. There were subpericardial and subarachnoid haemorrhages, and bleeding into the substance of the lungs and kidneys.

Death sometimes occurred in the subacute type of case either before ascites developed or before it was present in clinically detectable amounts.

Four patients were in coma for over two days and yet ultimately recovered. They were clinically of the subacute type and differed only in the final outcome from the fatal cases already described. Three were Indian and one British. It has been possible to follow up only the one British case, who was clinically well 12 months after emerging from coma.

Case R 3 Driver J, British, aged 20 years, had syphilis treated by penicillin in August 1945. He developed anorexia on 19 November and jaundice on 22 November. He was tender in the right hypochondrium and the liver became palpable on 26 November. There was normal progress till 29 November when he had a nightmare. On 30 November the liver was not palpable and the left ankle reflex was brisker than the right. On 1 December he had a small haematemesis and became drowsy. On 2 December the liver dullness was diminished. On 3 December he was stuporose and violent, purpura appeared on the shoulders and liver dullness was absent. Pupils were dilated and both ankle reflexes were exceedingly brisk. On 4 December he was comatose and incontinent. There was purpura on the legs, sustained left ankle clonus, and bilateral extensor plantar responses. On 5 December at 8 a.m. the liver dullness was present again, and at 9 p.m. coma lightened and he began to respond to heavy stimuli. On 6 December he was eating and drinking and all abnormal neurological signs had disappeared. On 7 December the liver was once again palpable and remained so until his evacuation from Burma on 19 December, by which time he was no longer jaundiced.

Hepatic biopsy by Dr S. P. V. Sherlock in November 1946 showed restoration of normal liver architecture.

Pathological Features

This investigation into the morbid anatomical and histological changes of liver necrosis in the course of infective hepatitis extended from October 1944 to June 1946, and comprised clinical and post-mortem records and fixed tissues from 45 fatal cases. Material from the first 12 cases came from Military Hospitals in Assam and Bengal, there were 33 further cases from Burma which form the main body of the work. Autopsy examinations were conducted soon after death, for the swift progress of autolytic changes in hepatic necrosis after death is well recognized (van Beek and Haex, 1943). The tissues were fixed in 10 per cent formol-saline. Paraffin sections were prepared and stained with haematoxylin and eosin. Liver sections were stained as a routine with Harris's acid haematoxylin and eosin and with Mayer's haemalum. Azocarmine and van Gieson's stain were used to demonstrate connective tissue, and reticulin fibres were stained by Wilder's or Foot's silver impregnation method. Owing to climatic conditions and delay in transport, post mortem autolytic changes were present in a number of the tissues.

Macroscopic appearances of the liver The gross anatomical features of the livers in the 45 cases under review are fairly typical of yellow atrophy, except in six cases with appearances rarely seen in human pathology. These were obtained from severe fulminating cases with marked haemorrhagic phenomena. Most of the livers were reduced in size, occasionally to an extreme degree, one quarter of the number being within normal limits, the remainder showing moderate or marked reduction. The usual figure for reduction was to 1,200 to 900 gm. The atrophy was irregular throughout the organ, the left lobe being sometimes reduced out of proportion to the right. In the acute cases the capsule was smooth over the whole surface of the organ or showed only localized or diffuse wrinkling, in a few of these livers there were fine folds along the anterior border of the right lobe or over the inferior surface. The colour varied according to the stage at which the disease terminated. In the fulminating haemorrhagic cases the colour of the right lobe was predominantly dark red, sometimes maroon, with patches of purple and yellow mottling (Plate 5, Fig 4). The left lobe was usually paler reddish-brown. At a later stage the colour was grey-red with large patches of yellow and green and the surface finely granular. In the advanced cases the appearances were typically fibrotic with yellowish-green nodules projecting above the surface of the organ (Plate 5, Fig 5). The consistency was usually soft and friable in the early stages, occasionally flaccid and even sponge-like. Later it became firm and in the nodular type tough and fibrous. The cut surface showed an equal variety of appearances. The lobular pattern was obscured or lost. In the livers from the fulminating cases, the general appearance was that of red meat-like tissue oozing blood, with patches of pale or brighter yellow. In one of the earliest cases the substance of the right lobe was mahogany coloured with patches of yellow, while the dome con-

sisted of black mushy pulp not unlike the appearance seen in an acute malarial spleen. This was due to massive haemorrhages. At a later stage and specially in the subacute cases, many of the livers revealed the characteristic features of yellow nodules of hyperplastic tissue against a background of red collapsed parenchyma. With regard to the relation of the size of the liver to the duration of disease, there was reduction at all stages with considerable variation. The two smallest livers in the series weighed 453 and 340 gm and were found in patients with illnesses lasting 19 and 25 days respectively. Of

TABLE V

Relation of Duration of Disease to Histological Stages in Fatal Infective Hepatitis

Duration of disease in days	Acute fulminating hepatitis	Acute hepatitis with repair	Early subacute hepatitis	Nodular hyperplasia	Diffuse hepatic fibrosis	Total
0 to 9	6	4	—	—	—	10
10 " 19	—	8	7	5	—	20
20 " 29	—	2	—	5	—	7
30 " 39	—	1	—	1	—	2
40 " 49	—	—	—	3	—	3
50 and over	—	—	—	1	2	3
Total	6	15	7	15	2	45

three cases with protracted illnesses from 69 to 116 days, one had a large liver and the other two were reduced as much as in those with shorter illnesses. Ascites was found in 35 per cent of the cases. It was usually associated with disease of some duration, but occasionally occurred early. As a rule the fluid was abundant, varying from two to 10 pints, it was turbid, bile-stained, and sometimes sanious. In one case with a history of 69 days over 10 pints were present.

Microscopic appearances of the liver. The main histological changes consisted of a diffuse hepatocellular necrosis and autolysis with leucocytic and histiocytic infiltration. In a number of the acute cases of short duration haemorrhage was a remarkable and unusual feature. The process of repair was demonstrated at all stages from the multiplication of a few surviving hepatic cells to the well-developed hyperplastic nodule and also in the proliferation of the bile-ducts. In a few of the more advanced cases residual fibrotic changes were marked. The histological features of the livers will now be studied in detail, and for convenience will be placed in groups according to the duration of the disease.

Acute fulminating hepatitis. There were six cases in this group. They appear to represent the most severe manifestations of the disease in its earliest and most acute phase. All came from South Burma, except one from South Bengal. Clinically they were characterized by short severe illnesses of under 10 days' duration. The histological pictures seen in these cases are illustrated in Plate 7, Figs. 8, 9, and 10, where the outstanding features are massive parenchymal necrosis combined with haemorrhages. These varied from small extravasations of blood or a few ruptured sinusoids

to widespread haemorrhages obliterating the entire lobular structure. Plate 7, Fig 10 shows a microscopic field taken from one of these areas in which the only surviving structures are those within the portal tracts. However, a more typical appearance is to find clusters of surviving liver cells in the portal zones or scattered haphazard throughout the tissue. There are narrow bands of hepatic tissue outlining or separating the haemorrhages, and frequently also disrupted by more haemorrhages producing the characteristic picture of islets of parenchyma surviving amid masses of haemorrhage (Plate 7, Fig 9). In a few instances the necrosis is seen with a zonal arrangement in which the greatest damage is around the central hepatic vein. The surviving liver cells stain faintly eosinophilic and show marked swelling and vacuolation of the cytoplasm. Where fatty degeneration is most marked, the hepatic cell in sections stained with haematoxylin and eosin appears as a network of vacuoles surrounding the nucleus. Binucleate cells are rarely seen and proliferating bile ducts are not found. The sinusoids in the surviving parenchyma are small and partly emptied by pressure from swollen hepatic cells as well as from adjacent areas of haemorrhage, proliferation of their endothelial lining is seen in many instances. The whole tissue is infiltrated with polymorphs, lymphocytes, histiocytes, and pigmented macrophages. There is a tendency for leucocytes to accumulate in the portal tracts. The histological picture in the fulminating case is one of extensive haemorrhages with acute diffuse hepatitis.

Acute hepatitis with evidence of repair. This type of histological picture was found in 15 cases with illnesses varying from 10 days to four weeks' duration. They are fairly typical examples of acute diffuse necrosis with evidence of regenerative activity in bile-ducts and hepatic cells. They have certain features in common with the fulminating cases. For instance, there are numerous haemorrhages involving large areas of the parenchyma, but the amount of activity in the surviving cells and in early proliferating bile ducts indicates a less severe type of lesion permitting efforts at compensatory hypertrophy. The initial lesion is in the centrilobular zone producing degeneration and autolysis of the cells around the hepatic vein, with a leucocytic and histiocytic reaction. The emptying of the lobule may be complete (Plate 7, Fig 11). A highly characteristic feature at this stage of the disease is the presence of a rim of surviving parenchyma or a few early proliferating bile-ducts outlining the periphery of the lobule. In spite of the extensive cell necrosis the reticulin framework is perfectly preserved. The depleted stroma is occupied by cytoplasmic and nuclear debris and a marked infiltration with exudative cells in which polymorphs, lymphocytes, plasma cells, and pigmented macrophages are found in variable proportions. There are also periportal accumulations of leucocytes, among which a few eosinophils may be seen. Endophlebitis is also associated with this stage of the disease. It was found in four livers, usually in the centrilobular vein, and in one the wall of the vein showed hyaline thickening and subendothelial infiltration with inflammatory cells.

Subacute hepatitis There is no fundamental difference between the acute and subacute forms of this disease. The subacute is the stage at which the hypertrophic activities among the surviving structures become the outstanding feature in the microscopic picture, it is characterized by proliferation of hepatic cells and bile-ducts and by organization of granulation tissue. In many of the acute cases clumps of binucleate liver cells have been observed as early as the tenth day and in a few cases probably earlier. In the group of cases about to be described large masses of new liver cells are found to appear by 18 to 20 days. This group comprises 25 cases in which three main histological pictures can be distinguished.

Early subacute hepatitis This type of picture was found in seven cases with illnesses of from 10 to 20 days' duration. They all show the classical features of bile-duct and hepatic cell proliferation with richly cellular granulation tissue. Plate 8, Fig 13 shows a field from a case of 10 days' duration in which early budding bile-ducts are seen outlining lobular remnants. In contrast the picture in Plate 8, Fig 12 taken from a case of 11 days' duration shows pronounced bile-duct proliferation occupying most of the microscopic field. Mitotic figures are found in the epithelium lining the ducts. On closer inspection small clumps of hyperplastic liver cells can be seen among the bile-ducts. These cells vary considerably in appearance, being larger than normal parenchyma and having hyperchromatic nuclei with prominent nucleoli, many are binucleate and occasionally multinucleate with a neoplastic appearance, in many instances the cytoplasm is bile-stained, appears vacuolated, and contains coarse granules of bile pigment. Blocking of the canaliculi by bile thrombi is commonly found. Sections stained with azocarmine and by van Gieson's method show little sign of increased connective tissue fibres at this stage. The stroma is still rich in cells, the majority of which are lymphocytes and histiocytes with large numbers of pigmented macrophages. Leucocytic infiltrations are abundant in the portal stroma. Small areas of the stroma are intensely hyperaemic.

Nodular hyperplasia At this stage the hyperplasia among groups of surviving cells has become extremely active, producing islands or nodules of new parenchyma. This type of lesion was found in 16 cases with illnesses of from 11 days to six weeks' duration. The general picture is characterized by gross parenchymal destruction with single or confluent hyperplastic nodules frequently found in the vicinity of the portal tracts, separated by fibrous stroma which contains numerous branching bile-ducts and exudative cells. The nodules are complete and compact and show no invasion by granulation tissue. They are composed of compact cords of liver cells and of isolated liver cells, there is no lobular symmetry. Many of them are markedly ischaemic and present a striking contrast to areas in the stroma which are intensely vascular (Plate 8, Fig 14). Hyaline and fatty changes are frequently seen in the hyperplastic epithelium, bile stained cells and bile thrombi in the intralobular canaliculi are fairly numerous. Further progress of the nodular lesion consists in breaking up of the nodule into small groups

of cells by extensions of granulation tissue (Plate 8, Fig 15) The granulation tissue becomes less cellular and even where there are still foci of cellularity, many of the cells are fibroblastic in character There is also considerable scarring around the portal tracts In the most advanced stage of this lesion, however, there are still numerous large hyperplastic patches of parenchyma unaffected by fibrous extensions

Diffuse hepatic fibrosis This is an unusual type of lesion to find in epidemic hepatitis, and was seen in two cases only Both were patients with protracted illnesses of 69 and 116 days' duration The histological pictures are similar but not identical There is no evidence of nodular hyperplasia There is gross distortion of the normal lobular architecture with atrophy, necrosis, and autolysis of the liver cell columns, though the peripheral lobular zones are well preserved The predominant lesion appears to be in the portal zones, as illustrated in Plate 9, Figs 16 and 17 There is a wide zone of periportal connective tissue with well-marked infiltration with lymphocytes, plasma cells, and polymorphs There are also moderate numbers of proliferating bile-ducts and numerous binucleate and multinucleate liver cells with prominent nucleoli Bile-stained cells are seen occasionally, also granules of bile pigment in the cytoplasm and bile thrombi in the intralobular canaliculi The lesion is seen extending around the lobules in the form of a peri-lobular cirrhosis Both pictures suggest a degree of chronicity which is more marked in Plate 9, Fig 17 than in Plate 9, Fig 16 In other parts of the liver shown in Plate 9, Fig 16 there is evidence of more acute changes as seen in small scattered areas in which there is marked sinusoidal engorgement and mild degenerate changes in the intervening liver cell columns These indicate more recent damage superimposed on a liver showing a considerable degree of repair In this connexion it is interesting to note that this patient (Case 7, whose clinical history is given in the discussion below) had a recurrence of hepatitis which ended fatally

Macroscopic and microscopic appearance of other organs *Gall-bladder* In the majority of cases the gall-bladder was normal in size or slightly reduced, and contained black viscid or watery green bile In two, however, both with nodular hyperplasia of the liver and one with phlegmonous inflammation of the colon, the gall-bladder was greatly swollen and tense One contained dark clotted blood which appeared to have come from the hepatic ducts, which had numerous petechiae on their mucosal lining The other gall-bladder contained a small amount of black bile, microscopically the wall showed hyperaemia and oedema and a scanty diffuse round cell infiltration which was most marked in the submucosa In two other cases there was slight oedema and congestion of the gall-bladder

Spleen In almost 70 per cent of the cases there was enlargement of the spleen Generally speaking the naked-eye and microscopic features were similar to those described by Lucké (1944) and Wood (1946), but in a number of the African and Indian cases there were pathological changes consistent with previous malarial infection There was perisplenitis and thickening

of the fibrous trabeculae, fibroblastic proliferation in the pulp cords and occasionally in the follicles, and varying amounts of black pigment visible microscopically. Smears from the pulp did not show malarial parasites. In the acute cases, including those of a fulminating character, the spleen was enlarged, soft, and boggy in parts, but as a rule little pulp could be expressed. At a later stage there was little difference in size, but the consistency was firmer. Histological examination of 17 spleens showed moderate or intense engorgement of the sinusoidal veins and pulp cords at all stages of the disease. In the early acute cases the lymphoid elements were prominent, appearing as large hyperplastic follicles with central oedema and occasionally small patches of necrosis. The lymphocytes in the reticulum were greatly in excess. At a later stage the picture was dominated by engorged sinusoids and many of the lymphoid follicles had become small and hypoplastic, there was also fibrosis throughout the tissue. A striking feature observed in two cases only was marked dilatation of the sinusoids which appeared to have gaping, thickened walls (Plate 10, Fig. 19).

Gastro-intestinal tract The condition described by Lucke (1944) as phlegmonous inflammation of the colon and duodenum was found in four cases in the present series. These were all cases of nodular hyperplasia of the liver associated with ascites (Plate 6, Figs. 6 and 7). Histological examination showed intense congestion, oedema, and cellular infiltration into all coats. The submucosa was greatly distended by oedema, haemorrhages, and an abundant exudate of polymorphs, histiocytes, plasma cells, and eosinophils (Plate 10, Fig. 18). There were two more cases in the series which showed non-inflammatory oedema of the large and small intestines. They, too, were associated with nodular hyperplasia of the liver and with ascites.

Kidneys The kidneys sometimes showed cloudy swelling, but no other change.

Suprarenals As a rule the suprarenals presented no naked-eye abnormality apart from congestion of the superficial blood-vessels and in three cases pinpoint haemorrhages under the capsule. Six were examined histologically. Of these, three were normal, while the others showed definite lesions in the outer and middle zones of the cortex. There was marked congestion and numerous small subcapsular haemorrhages. There were varying degrees of fatty degenerative changes in the parenchyma cells, which in some instances had gone on to necrosis. In one of these cases (a case of nodular hyperplasia of the liver associated with ascites) a few of the necrotic patches in the cortex were infiltrated with lymphocytes, plasma cells, and polymorphs (Plate 10, Fig. 20). No bacteria were seen.

Brain The brain often showed oedema of the white matter and occasionally small extravasations of red blood-cells and perivascular round cells in the basal meninges and ganglia.

Haemorrhagic phenomena Macroscopic haemorrhages in the form of petechiae or large purpuric patches were found in a number of organs other than the liver, and appeared at all stages of the disease. They were seen

commonly in the lungs, intestines, and heart, and less frequently in the kidneys, adrenals, pancreas, and brain. Haemorrhages in the heart were frequently located along the course of the coronary arteries and in clusters at the left auriculo-ventricular junction.

Summary of pathological features The gross anatomical features of the livers were fairly typical of yellow atrophy, except in six cases of fulminating hepatitis in which haemorrhagic phenomena were marked. The livers in these cases were predominantly dark red in colour, sometimes maroon, and showed prominent patches of purple and yellow. In one case the dome of the right lobe was soft and sponge-like as a result of massive haemorrhage. In the majority of cases there was reduction in size of the liver, occasionally to a marked degree. In the acute fulminating case the histological picture was one of extensive haemorrhages with acute diffuse hepatitis. In a few instances the haemorrhage was so extensive that the entire lobular architecture was obliterated, leaving only the portal tracts. In most of the cases the cellular infiltration was maximal in the portal zones. Fifteen cases presented the features of acute diffuse hepatitis with commencing regenerative activity in bile-duct and hepatic epithelium. In 22 subacute cases the process of repair was demonstrated at all stages from the multiplication of a few surviving hepatic cells to the well-formed hyperplastic nodule, and also in the proliferation of bile ducts and the organization of granulation tissue. It is noted that nodulation may appear by 18 to 20 days. An unusual histological picture was found in two longstanding subacute cases, this has been described as a diffuse hepatic fibrosis. Here the predominant lesion was in the portal zones. There was increased fibrosis with a cellular reaction and bile-duct proliferation. This lesion is seen extending around the lobule in the form of a perilobular fibrosis. The gall-bladder was enlarged and tense in two cases only. Microscopically there was oedema and in one a mild inflammatory reaction in the wall.

In the majority of cases the spleen was enlarged. In the acute cases the enlargement was considered to be the result of hyperaemia and of lymphoid hyperplasia. Later in the disease the sinusoidal engorgement was more marked and this may have been the result of portal hypertension. Four cases showed phlegmonous inflammation of the intestinal tract and two others a non-inflammatory oedema of the gut. This is regarded as a terminal lesion. Interstitial pancreatitis was found in one case only and was associated with phlegmonous inflammation of the duodenum. The kidneys sometimes showed cloudy swelling. A patchy necrosis of the suprarenal cortex was found in three cases of the six examined histologically, and in one of them there was infiltration with inflammatory cells. Histological examination of the brain revealed hyperaemia, small perivascular haemorrhages, and oedema. Haemorrhagic phenomena were prominent features in the lungs, intestines, and heart, small patches of subarachnoid haemorrhage were not infrequently found.

Discussion

Before discussing the possible implications of this series of cases, it is important to be certain that they did in fact die of hepatic necrosis consequent upon infective hepatitis and not of some other disease. Occasional proven cases of Weil's disease occurred during the period under review, and steps were taken to exclude this possibility, though the absence of suffusion of the eyes or severe body pains, of oliguria or leucocytosis, and often of fever, made it unlikely. Spirochaetes were never recovered from the blood nor from fresh alkaline urine. Owing to the shortage of experimental animals, guinea-pig inoculation, which had proved negative on five early cases in the series, was discontinued. The final exclusion rests on pathological grounds. The livers in our cases were usually small, occasionally normal in size, but never large, and their histology was similar to that found by Dible, McMichael, and Sherlock (1943) in biopsies from cases of infective hepatitis. Hutchison, Pippard, White, and Sheehan (1946), in a discussion of 17 cases of Weil's disease occurring in Italy, considered that the possibility of confusion between leptospirosis and infective hepatitis is remote, in their cases the liver at autopsy showed no histological trace of recent or healing necrosis nor degeneration of hepatic cells. The occurrence of yellow fever in Burma has not yet been recorded. If the virus were introduced, the disease might be expected to spread at an alarming rate and the number of reported cases of jaundice to rise rather than fall as they did. The final exclusion rests once again on histological grounds. No Councilman lesions were ever seen in the sections of these livers. In no case was there any evidence of poisoning by chloroform, cinchophen, mushrooms, or bacterial toxins. Two cases had received carbon tetrachloride in what proved to be the pre-icteric phase of infective hepatitis on account of concurrent ankylostomiasis. The livers of both these cases showed histological changes indistinguishable from those seen in the other cases in the series. In both cases there was an interval of a week between the administration of carbon tetrachloride and death, in other words, the exhibition of the drug was not followed by a dramatic onset of the final phase. It cannot be denied, however, that it may have acted as an additional toxipathic factor (Himsworth and Glynn, 1944*b*), whose summation with the toxipathic factor of infective hepatitis was sufficient to cause hepatic necrosis. The exclusion of these various factors leaves little doubt that the series of cases described did in fact die of hepatic necrosis complicating infective hepatitis.

Cause of the high death-rate. The possible causes of the high mortality, five or six times the rate usually recorded, must now be considered. This can be explained on one of two bases, firstly, a postulate of some additional factor which produced liver damage in the population at risk in South Burma alone, particularly in Rangoon, and whose effects by summation with the damage of infective hepatitis might lead to hepatic necrosis, and secondly, a local variation of the virulence of the causative organism of infective hepatitis itself.

Mepacrine The whole of the population at risk was on a regime of suppressive mepacrine consisting of 0.1 gm daily. There is some experimental evidence that mepacrine may produce liver damage in animals. Wright and Lillie (1943) have described necrotic areas in the livers of rats fed on atabrine, and Silber, Clark, and Siegel (1944) have correlated the degree of hepatic necrosis produced with the blood level of atabrine attained and the duration of its maintenance. Macgrath and Havard (1945), however, found no evidence of liver dysfunction in volunteers who had been on mepacrine 0.1 gm daily for 12 months, though liver biopsies were not done on these cases. Drew and Reid (1945) have found normal liver structure at biopsy in 10 men who had been on suppressive mepacrine from six to 17 months. On the other hand, Agress (1946) recorded five cases of mepacrine sensitivity in 3,000 Chinese troops. They all had exfoliative dermatitis and three died. Their livers showed 'areas of necrosis' in two cases and a 'diffuse necrosis' in the other. No photomicrographs were published and the evidence that this liver damage followed the ingestion of mepacrine is not certain, for three of the cases had septic wounds with fever, and one had a fever of undetermined origin for 37 days. Hundreds of thousands of men have been on suppressive mepacrine for long periods in many parts of the world during the recent war, yet the mortality rate reported in those of them who developed infective hepatitis has been of the usual order. Mepacrine cannot be blamed for the high death-rate observed in South Burma.

Nutrition Much attention has recently been focused on the role of deficient nutrition in the production of liver damage. Himsworth and Glynn (1944c) have shown that rats fed on a low protein diet develop massive necrosis of the liver, and cited Muwazi and Trowell's (1942) observations in East Africa as affording a human corollary to this experiment. They have also shown that this necrosis may proceed to a cirrhosis such as has been seen on the Rand and in the Punjab in undernourished natives (Gillman, 1944, Hughes, 1926, 1933, Hughes and Shrivastava, 1927). They have confirmed Daft, Sebrell, and Lillie's (1942) findings that methionine has a preventive action against the production of hepatic necrosis in such rats. Prigosen and Gordon (1942) considered that hepatic necrosis in man may be the result of infective or toxic factors on liver cells previously weakened by nutritional disturbance, and Himsworth and Glynn (1944b) suggested that massive necrosis occurring during the course of infective hepatitis may be due to nutritional factors. This contention receives support from Fox, Manso, Penna, and Pará (1942), who reported a death-rate of 2.4 per cent from infective hepatitis in undernourished Brazilians. Himsworth (1944), while admitting that there is no indication that the incidence of infective hepatitis could be influenced by diet, suggested that a high-protein diet or methionine might prevent the complication of hepatic necrosis. Wilson, Pollock, and Harris (1945) pointed out that the rarity of this complication would make it very difficult to decide the question. They found that there was a slight

bias in favour of giving methionine in an attempt to mitigate the severity of an attack of infective hepatitis, but their results were not statistically significant and they did not consider that dietary deficiency is a factor in determining the course of infective hepatitis in England. Finally, MacCallum and Miles (1946) reported that the inoculation of blood and faeces from patients with infective hepatitis into rats on a protein-deficient diet, followed by blind passage of the tissues of these rats, has led to the production of necrosis of the liver, enlargement of or haemorrhage into regional lymph-nodes, and haemorrhages into the stomach, gut, and lungs. Passage, titration, neutralization, and filtration experiments have suggested that this was a transmissible disease caused by a virus. This exceedingly important finding at present awaits confirmation.

The deaths in Burma may now be examined in the light of these facts. The histological pictures of the livers from these men show a series of changes from acute necrosis of liver cells with much haemorrhage to regenerative nodules and bile-duct proliferation. Zonal and diffuse types of lesion are encountered, but the whole of the liver is invariably affected to a greater or lesser degree. The appearances are those of a severe toxipathic hepatitis. There was in no case evidence of a localized massive necrosis of a trophopathic kind described by Himsworth and Glynn (1944*a*) as following deficiency of methionine. It is true that in four cases the left lobe appeared to be more severely damaged than the remainder of the liver, which might conceivably suggest a trophopathic element in the necrosis according to Himsworth and Glynn's views. Malnutrition certainly occurred among some Indian troops in Burma between July 1945 and January 1946, these troops included many strict vegetarians who refused to take meat, fish, or eggs, though they would sometimes eat cheese. They were commonly grossly anaemic and would walk into hospital with less than 1,000,000 red cells per c mm of blood, and many had diarrhoea and were heavily infested with a variety of worms. The combination of these factors not infrequently encompassed their death, and it can safely be said that these men were deficient in most dietary respects. Nevertheless, the livers of those who died showed no evidence of hepatic necrosis, and those of them who developed infective hepatitis ran a normally mild course. This confirms previous experience in Assam where malnutrition was prevalent both in Indian troops during the aftermath of the retreat from Burma in 1942 and in British troops on the return of Wingate's 1944 expedition. On the other hand, none of the fatal cases of infective hepatitis showed any clinical signs of malnutrition. It remains to be said that there were ration cuts of various food-stuffs both in North and South Burma between mid-August 1945 and March 1946. They changed from week to week, affected British troops almost exclusively, and a cut in one type of food was often counteracted by an increase in another. Analysis showed no material difference between the methionine content of the diet in the two areas. There were no greater opportunities for supplementing the diet in North than in South Burma.

The concentration of fatal cases around Rangoon cannot be explained on a nutritional basis

The difficulty which besets the ready acceptance of an increased virulence of the virus in this outbreak is the crossing of the graphs of attack rates and mortality rates. The former fell while the latter rose, and this is in contrast to the usual occurrence in previously recorded epidemics. It must be remembered, however, that the fighting in Burma came to an end during the period under review, and the declining attack rate of infective hepatitis may be explained by the steadily improving sanitation. If the falling attack rate is regarded as the result of better hygiene, the crossing of the graphs no longer presents an insuperable obstacle to the acceptance of the explanation of increased virulence. It must be concluded that there was a virulent local strain of the infective hepatitis virus in South Burma, particularly in Rangoon. Fatal cases of infective hepatitis occurred in Assam, Singapore, Bangkok, French Indo-China, and Hong Kong between July 1945 and June 1946, 11 in all. They have nearly all conformed to the subacute course described above, and suggest that the high incidence of severe hepatitis in Burma was reflected by an increased virulence of the virus throughout South-East Asia.

Recurrences. There remains one question of some importance which demands an answer. What is the factor which determines the onset of the final phase in the subacute type of case? Clinically this phase resembles that seen in the acute type of death except in the presence of ascites (which is an incidental finding due to increased portal pressure and in no way specifically related to infective hepatitis) and in its duration, which is slightly more prolonged than that seen in the acute type. The gross histological findings in the livers of those who died in the subacute stage are similar to those found by Dible, McMichael, and Sherlock (1943) at biopsy by Iversen and Roholm's (1939) technique in patients with infective hepatitis pursuing a normal course, although there is a much heavier necrosis of the regenerated liver cells. The latter may be partly explained by ischaemia in the case of large nodules of new parenchyma, but ischaemia can play no part in the secondary necrosis of small clumps of regenerating cells. There is some factor which causes a sudden accession of damage in a liver whose essential histology is that of normal repair. An extraneous factor may be recognized in some cases. In two cases in the present series it is possible that a therapeutic dose of carbon tetrachloride was the precipitating factor. In most cases, however, there was no known extraneous cause, and it is most probable that the factor involved was a recurrence of infective hepatitis caused by the same virus that produced the initial attack. Recurrences are a well-known feature of the disease. Witts (1944) estimated that they occur in 2 per cent of cases and this concurs with the main body of opinion (Findlay, Martin, and Mitchell, 1944, Hoagland and Shank, 1946), though Peters, Thompson, King, Williams, and Nicol (1945) observed 30 relapses in 468 cases of post-arsphenamine jaundice. They also noted that 26 of these

relapses occurred in 150 cases whose initial attack was considered on clinical grounds to be severe, while the remaining five relapses followed light attacks of hepatitis. Marshall (1943) suggested that recurrences are due to superinfection from other cases of infective hepatitis treated in the same ward. Most of those he observed occurred after about 30 days and this is his main argument, but other experience of the time relations of recurrences does not coincide with his. The fact that one attack of infective hepatitis confers a high degree of immunity also makes superinfection improbable. Autoinfection with the same virus that caused the initial attack is much more likely to cause the recurrence.

Virus diseases, both in animals and plants, are noted for the persistence of the causal organism in the host in the absence of symptoms. It is probable that infective hepatitis provides no exception to this general rule, and that the virus remains hidden in the gut between recurrences. Attempts to demonstrate this have so far failed (Neeffe, Stokes, and Remhold, 1945; Havens, 1946), though recent work has emphasized the faecal mode of spread of the disease (Findlay and Martin, 1943; Findlay, Martin, and Mitchell, 1944; MacCallum and Bradley, 1944). There is a suggestive parallel in the case of anterior poliomyelitis, whose virus has been demonstrated in the gut for periods up to four months after recovery from symptoms (Lépine, Sédallian, and Sautter, 1939; Paul, 1941; Paul and Trask, 1941, 1942).

Fibrosis of the liver. The evidence that cirrhosis may follow infective hepatitis is considerable. Cases have been recorded by Cullinan (1936), Polack (1937), Krarup and Roholm (1941), and Rennie (1945). Pathological studies by Ratnoff and Patek (1942) suggested that 6.5 per cent of 386 cases of cirrhosis were due to infective hepatitis, and five of 16 cirrhoses observed by Rennie (1943) gave a history of infective hepatitis and no other possible causative factor. Higgins, O'Brien, Stewart, and Witts (1944) regarded all jaundice lasting longer than two months as indicating a subacute hepatitis which renders the patient a prospective candidate for subsequent scarring. Luck's (1944) objection that infective hepatitis and cirrhosis of the liver are both common diseases and that a previous history of hepatitis in a cirrhotic patient does not necessarily imply a causal relationship is valid, but it must be remembered that subicteric attacks of infective hepatitis frequently remain undiagnosed and, in such cases, will not be forthcoming in the history. In this connexion the term cirrhosis demands closer definition, for it is probable that the course of the process in the liver when an attack of infective hepatitis leads to a nodular hyperplasia on the one hand and to a multilobular cirrhosis on the other is very different. In most reports of cirrhosis after infective hepatitis the distinction between nodular hyperplasia and multilobular cirrhosis (or diffuse hepatic fibrosis) is not made. This is not surprising, for in their later stages the two conditions may be exceedingly difficult if not impossible to distinguish. Experimental evidence goes to show that the liver is capable of complete recovery from a

single attack of severe damage, but is less likely to do so if subjected to repeated minor damage (Whipple and Sperry, 1909, Cameron and Karunaratne, 1936) Multilobular cirrhosis might be expected after recurrent attacks of infective hepatitis, and it may well be that patients with a definite association of infective hepatitis and multilobular cirrhosis have had recurrences of a subicteric and unrecognized type One case in the present series illustrates what may be an intermediate stage in the production of a diffuse hepatic fibrosis by repeated recurrences of infective hepatitis

Case 7 Major A, British, aged 31 years, had complained of periodic lassitude in India and Ceylon since May 1945 The first definite symptoms appeared in September 1945 when he went off his food completely and developed jaundice He was admitted to hospital in Rangoon, treated for infective hepatitis and discharged with apparent clinical cure on 15 October He was readmitted on 25 October on account of oedema of ankles and face and continued lassitude He was tender in the right hypochondrium, but the liver was not palpable, nor was the spleen There was slight jaundice and bile pigments were present in the urine Serum-proteins were 5.0 gm per 100 c.c. He bled from his gums on 28 October, and on 30 October there were signs of ascites and he vomited altered blood There were cutaneous petechiae On 1 November he was transfused, since his red cells were only 2,500,000 per c.mm. Serum-bilirubin was 0.2 mg per 100 c.c. On 3 November jaundice deepened, ascites increased, and he complained of pain in the right side By 15 November his abdomen was grossly distended, serum-bilirubin was 20 mg per 100 c.c., there were widespread cutaneous petechiae, and he was drowsy He died in coma on 16 November

Autopsy All subcutaneous tissues were waterlogged A normal-sized liver with smooth capsule and yellow and purple mottling Sections showed widespread centrilobular necrosis, regenerating liver cells, bile-duct proliferation, and a cellular reaction most marked around the portal tracts There were areas of intense congestion, and a diffuse fibrosis (Plate 9, Fig 16)

In discussing this possibility it must be emphasized that the liver at autopsy in the majority of the longstanding cases showed a frank nodular hyperplasia, not a diffuse hepatic fibrosis It is suggested that one severe attack of hepatitis may produce nodular hyperplasia, while repeated mild attacks may result in diffuse hepatic fibrosis of a multilobular type The latter process may be interrupted by death at any stage if a recurrence is severe enough to raise the degree of liver damage above the critical level

It seems that the possible reactions to an attack of infective hepatitis may be summarized as follows

- 1 The usual signs of anorexia and tender liver, with or without jaundice, resulting in complete recovery
- 2 Death within a few days from acute hepatic necrosis with the symptom-complex of cholaemia
- 3 The usual signs of infective hepatitis with recovery, followed by a recurrence which presents the same features as the initial attack and results in recovery
- 4 The usual signs of infective hepatitis with recovery, followed by a recurrence which causes death from subacute hepatic necrosis

5 A clinically severe attack of infective hepatitis with recovery and the development of nodular hyperplasia

6 The usual signs of infective hepatitis, followed by apparent recovery (with, probably, subicteric recurrences), and the late appearance of diffuse fibrosis

Summary

1 An outbreak of severe infective hepatitis in Burma is described

2 Acute and subacute modes of death are distinguished and an attempt is made to correlate the pathological findings with the duration of disease

3 Possible causes of the high mortality rate in the outbreak are considered

4 The mechanism of death in the subacute type of case and the courses run by infective hepatitis are discussed

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Addendum

Since the present article was completed, Lucké and Mallory (1946) have reported what they describe as the Fulminant Form of Epidemic Hepatitis occurring in American forces in various theatres of war between 1943 and 1945. Their paper lends weight to the belief that the fulminating cases are in fact a form of infective hepatitis, and supports the view that their occurrence is due to increased virulence of the causal organism.

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FIG. 4. Case 16. Duration of disease eight days. Fulminating hepatitis. Liver reduced in size. Smooth capsule. Homogeneous surface, deep red colour with subcapsular and parenchymal haemorrhages.



FIG. 5. Case 26. Duration of disease 17 days. Nodular hyperplasia. Liver weighed 1,470 gm. Wide spread efforts at regeneration have resulted in a grossly nodular liver whose grey red stroma is unevenly studded with masses of hyperplastic parenchyma.

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FIG. 4. Case 16. Duration of disease eight days. Fulminating hepatitis. Liver reduced in size. Smooth capsule. Homogeneous surface, deep red colour, with subcapsular and parenchymal haemorrhages.

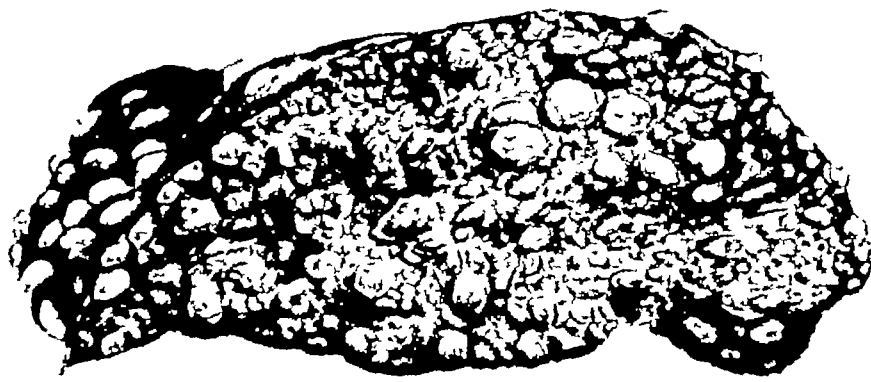


FIG. 5. Case 26. Duration of disease 17 days. Nodular hyaloplasm. Liver weighed 1.470 gm. Widespread efforts at regeneration have resulted in a grossly nodular liver whose grey red stroma is unevenly studded with masses of hyperplastic parenchyma.



FIG. 6. Case 18. Duration of disease 70 days. (Liver showed nodular hyperplasia.) Colon whole circumference spread flat after one longitudinal incision showing bulging folds of gelatinous oedema distorting the mucosal pattern.

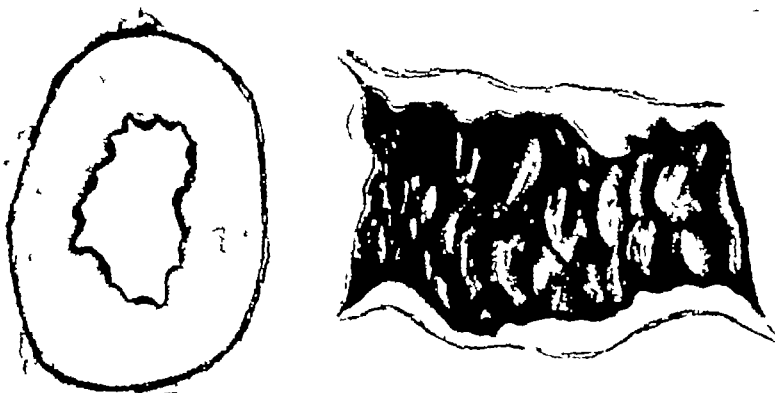


FIG. 7. Case A. 20. Duration of disease 25 days. (Liver showed nodular hyperplasia.) Colon in transverse and sagittal section showing deep red swollen oedematous mucosa.

(Figs. 4 to 7 are photographic reproductions of water colour paintings made by one of the authors (J. I. S.) immediately after autopsy.)



FIG. 8. Case 15. Duration of hepatitis six days. Large distended sinusoids and a few haemorrhages replacing parts of a lobule. A few surviving cells with marked fatty degenerative changes seen around a portal tract; some of these are so intensely vacuolated that they resemble foam cells. $\times 142$.



FIG. 9. Case 38. Duration of hepatitis five days. Massive haemorrhages and islets of surviving parenchyma. $\times 118$.

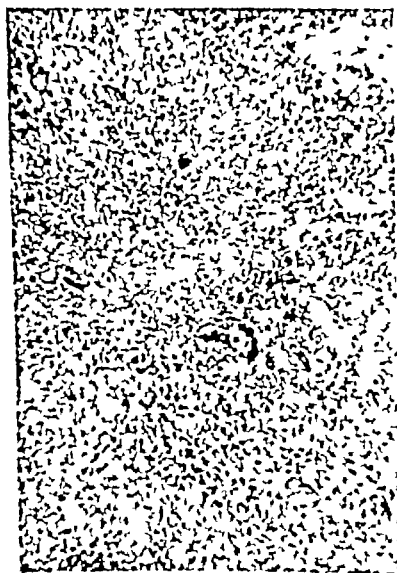


FIG. 10. Case 16. Duration of hepatitis eight days. Massive haemorrhages obliterating the entire lobular architecture. The only surviving structures are the portal tracts. $\times 118$.



FIG. 11. Case 20. Duration of hepatitis 11 days. Complete destruction of the lobule with a few early bile ducts outlining the periphery. The stroma contains cellular debris and leucocytic infiltration. $\times 118$.

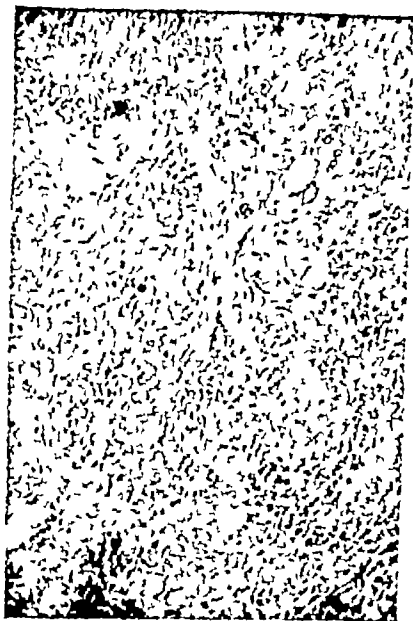


FIG 12 Case 3 Duration of hepatitis 11 days An area in which hepatic cells have been almost completely destroyed and the stroma is occupied by masses of proliferated bile ducts A few clumps of surviving liver cells have taken on proliferative activity $\times 44$



FIG 13 Case 21 Duration of hepatitis 10 days The lobular remnants are more or less outlined by small proliferating bile ducts $\times 80$



FIG 14 Case 37 Duration of hepatitis 18 days A typical picture of nodular hyperplasia An extremely vascular and cellular stroma surrounding islets of new parenchyma There is no lobular arrangement $\times 44$

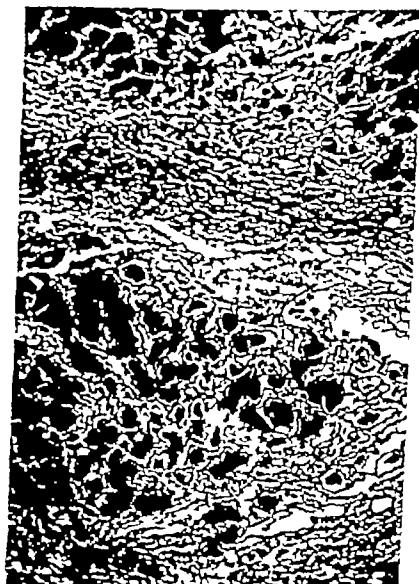


FIG 15 Case 26 Duration of hepatitis 17 days Two nodules of regenerated parenchyma invaded and split up by fibrous tissue There is condensation of the fibres between the nodules (Wilder's reticulum stain) $\times 122$

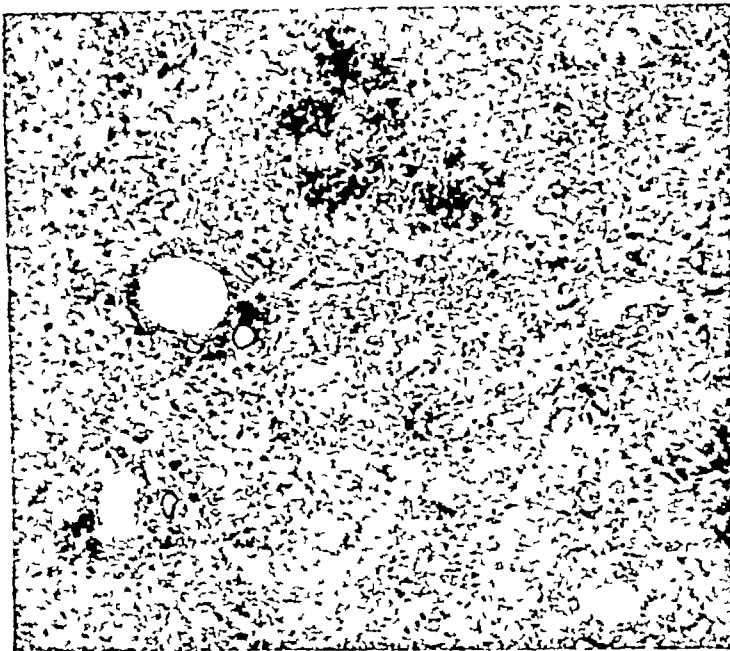


FIG. 16. Case 7. Duration of hepatitis 96 days. Diffuse hepatic fibrosis. A wide zone of periportal connective tissue with proliferated bile ducts and a moderate cellular reaction. The lesion is seen extending around the lobules. $\times 60$.

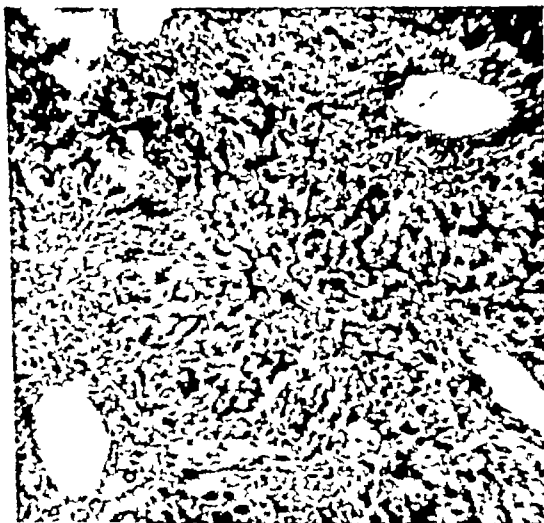


FIG. 17. Case 8. Duration of hepatitis 116 days. Diffuse hepatic fibrosis. Marked periportal fibrosis with leukocytic infiltration and new bile duct formation. The lesion is seen extending from four portal tracts and surrounding a lobule. $\times 100$.

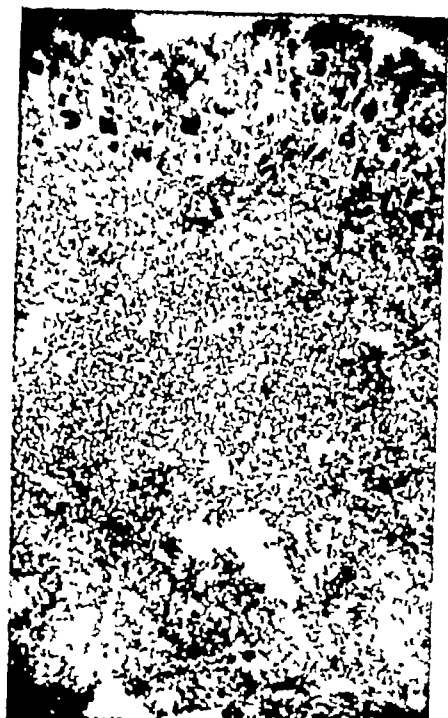


FIG. 18. Case A. 20. Duration of hepatitis 25 days. The colon showing phlegmonous inflammation. The submucosa is greatly distended with oedema, haemorrhages, and inflammatory exudate. The mucosa is intact. $\times 44$.

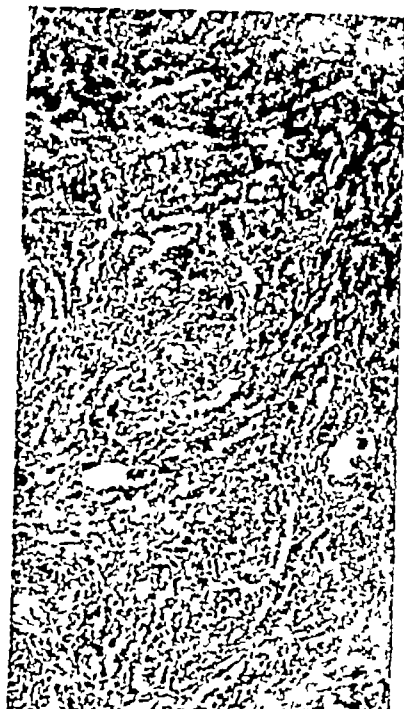


FIG. 19. Case 2. Duration of hepatitis 21 days. The spleen showing dilatation of the sinusoids. $\times 74$.



FIG. 20. Case 17. Duration of hepatitis 41 days. Suprarenal showing patchy necrosis of the cortex. A few of these areas are infiltrated with lymphocytes, plasma cells, and polymorphs. $\times 122$.

THE EFFECT OF THE INJECTION OF ACETYLCHOLINE INTO THE BRACHIAL ARTERY OF NORMAL SUBJECTS AND PATIENTS WITH MYASTHENIA GRAVIS¹

By ANDREW WILSON AND H. BERRINGTON STONER

(From the Departments of Pharmacology, Therapeutics, and Pathology, University of Sheffield, and the Royal Sheffield Infirmary and Hospital)

IN the light of current views on neuromuscular transmission there are at least three possible explanations for the phenomena of myasthenia gravis, namely excessive cholinesterase activity at the myoneural junction, the insufficient production of acetylcholine at the motor end-plate, or the interference in the normal action of acetylcholine by substances with a curare-mimetic action. In our previous work (Wilson and Stoner, 1944) we have been chiefly concerned with the first and last possibilities, and our results have led us to believe that substances of a curare-mimetic nature are circulating in the plasma of these patients. No systematic study of the second possibility was undertaken, but it was shown that patients with myasthenia gravis reacted normally to the subcutaneous injection of pilocarpine, which supports the clinical evidence that where acetylcholine has a muscarine effect it is produced in normal amounts. Attempts to supplement a supposedly inadequate production of acetylcholine at the motor nerve endings by giving acetylcholine by subcutaneous or intramuscular injection have usually proved unsuccessful (Cooke and Passmore, 1936, Kennedy and Wolf, 1937, Kolb, Harvey, and Whitehill, 1938, Bennett and Cash, 1943), although Fraser, McGeorge, and Murphy (1937) reported improvement in muscular power after large doses. The failure of these attempts is not surprising in view of the rapid destruction of acetylcholine in the body. It is doubtful if acetylcholine given by these routes would ever reach the desired point of action in an active form. Consequently, in order to test the hypothesis that there is insufficient production of acetylcholine in myasthenia gravis as in denervated muscle, with resultant hypersensitivity to injected acetylcholine, the principle of close-arterial injection as used in animal experiment has been applied to man. This was first done by Lanari (1937), who injected 40 mg. of acetylcholine into the brachial arteries of two patients with myasthenia gravis and observed a powerful contraction of the fore-arm muscles similar to that which occurred after a similar injection in patients in whom these muscles were denervated. This type of response was not seen in normal subjects where the intrabrachial injection of acetylcholine in this dosage produced no nicotine effects (Battro and Lanari, 1936). These findings were more fully

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investigated by Harvey, Lihenthal, and Talbot (1941), who studied the response to the intrabrachial injection of 10 to 50 mg of acetylcholine in 20 normal subjects. They found that the injection was followed by vasodilatation and sweating in the extremity. These features were accompanied by severe pain, which passed down the fore-arm into the hand, and a sensation of forceful flexion of the fingers, palm, and wrist, although no movement was

TABLE I

The Nicotine Effects seen after the Injection of Acetylcholine into the Brachial Artery of Normal Subjects

Case	Dose (mg)	Muscle action	Involuntary	Controllable	Muscle power	Fasciculation
20	40	None	—	—	Loss	Slight in flexor muscles of fore-arm
21	40	Flexion of fingers with adduction of thumb	Yes	Yes	No change	Absent
22	40	None	—	—	" "	"
23	40	"	—	—	" "	"
24	40	"	—	—	" "	"
25	40	Flexion of medial 3 fingers for 10 sec	Yes	No	Loss for 2 min	"
26	40	None	—	—	Slight loss after 1 min for 1 min	"
27	40	Slight flexion of fingers	Yes	Yes	Slight loss	"
28	40	None	—	—	Very slight loss	"
29	40	Adduction of thumb and slight flexion of fingers	Yes	Not the adduction	Slight loss	"
30	40	Slight adduction of thumb	"	Yes	" "	"
31	40	Slight adduction of thumb	"	"	No change	"
32	40	Adduction of thumb, followed by marked flexion of the fingers at the metacarpophalangeal joints	"	No	Loss	"

seen. Not only did no movement occur, but the hand became partially paralysed so that the power of the grip was reduced and the fingers could be only feebly flexed. Movement was seen in only one subject and on four occasions fasciculation occurred. These effects were attributed to an excess of acetylcholine at the motor nerve endings. In eight cases of myasthenia gravis Harvey and Lihenthal (1941) found that although the muscarine effect and sensory changes were the same as in normal persons, a vigorous motor spasm occurred instead of the transient paresis. The spasm consisted of vigorous flexion of the fingers, hand, and wrist, occurring a few seconds after

the injection and lasting 10 to 15 sec. There was no change in the power of the grip of the hand after the contraction had passed off, nor was any fasciculation seen. These authors concluded that in myasthenia gravis the production of acetylcholine is reduced, thereby resembling a state of functional denervation. In view of the importance of these results in the solution of the problem of myasthenia gravis and since this is the only finding at

TABLE II

The Nicotine Effects seen after the Injection of Acetylcholine into the Brachial Artery of Patients with Myasthenia Gravis

Case	Dose (mg)	Muscle action	Involuntary	Controllable	Muscle power	Fasciculation
1	40	Flexion of 3 medial fingers	Yes	Yes	Slight loss	Absent
3	40	Flexion of all fingers and thumb	"	Yes except 3rd and 5th fingers	No change	"
4	10	None	—	—	" "	"
4	80	Flexion of fingers	Only first finger	Yes	Loss	"
6	40	None	—	—	No change	Present
7	40	"	—	—	" "	Absent
8	30	Flexion of fingers	Yes	No	Loss	"
9	35	None	—	—	No change	"
12	40	Slight flexion of little and ring fingers	Yes	Yes	Loss	"
15	40	None	—	—	No change	"
16	30	Flexion of fingers	Yes	No	" "	"
17	40	None	—	—	" "	"
18	10	"	—	—	" "	"
18	40	"	—	—	Slight increase	"
18	80	"	—	—	No change	"

variance with the view that the threshold to acetylcholine is raised in myasthenia gravis, we decided to repeat these experiments.

Method

The technique of Lanari (1937) and Harvey, Lihenthal, and Talbot (1941) was used. Solutions of acetylcholine were freshly prepared by dissolving the appropriate dose in 2 c.c. of sterile saline. The skin over the brachial artery at the elbow was anaesthetized with 2 per cent procaine which was also infiltrated into the tissues around the artery. The needle of the syringe was introduced into the artery, the artery manually occluded above the site of injection, and after rapid injection of the solution of acetylcholine the occlusion was released. The nicotine effects, flexion, loss of muscle power and fasciculation, and the muscarine effects, vasodilatation, and sweating, were then observed in the injected extremity. Subjective sensations and complaints of pain were also recorded. The observations were made on 13 normal subjects and 12 patients with myasthenia gravis not under the influence of prostigmine.

Results

The nicotine effects seen in the normal subjects and in the patients with myasthenia gravis after the injection of acetylcholine are recorded in Tables I

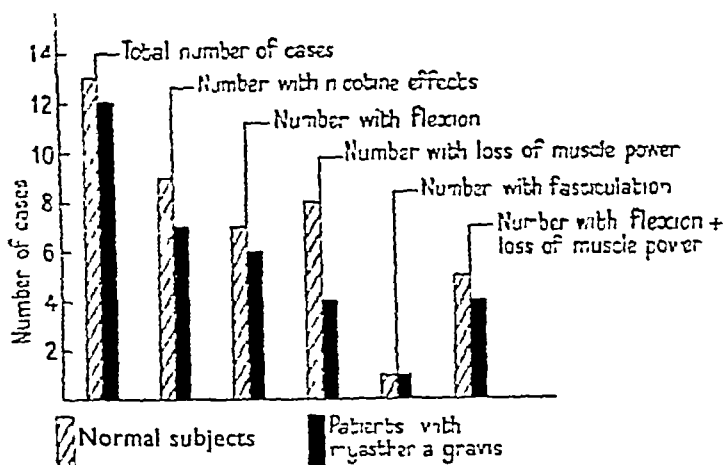
TABLE III

The Muscarine Effects seen after the Injection of Acetylcholine into the Brachial Artery of Normal Subjects and Patients with Myasthenia Gravis

Case	Dose (mg)	Arm	Flush			Sweating	Pain
			Forearm	Hand	Fingers		
Normal subjects							
20	40	R	—	—	+	+++	None, forearm numb
21	10	R	+	+	—	+	Cried out, forearm and fingers numb
22	40	L	—	+	—	+	None
23	40	R	+	—	—	—	Tingling as if fingers and wrists were pulled up
24	40	R	+	—	—	—	Tingling and slight pain in fingers
25	40	R	+	+	—	+	Severe, 'like red hot bar', as if arm pulled up
26	40	L	+	—	+	+	None
27	40	R	+	+	+	+++	None, arm felt dead
29	40	L	+	+	+	+	Pins and needles
30	40	R	+	+	+	+	Severe, like hand cut off
31	40	R	+	+	+	+	None
32	40	L	+++	+++	+++	+++	Moderate in forearm and back of hand
28	40	R	+	+	+	+	None
Patients with myasthenia gravis							
1	40	R	+	—	—	++	Severe pain forearm Choking sensation
3	40	L	++	—	+	++	None, as if wrist drawn up
4	10	L	+	+	+	++	Moderate in forearm and fingers
4	80	L	+++	++	+++	+++	Severe pain, fingers and wrists, as if wrist pulled up
6	40	L	+	+	+	+	None
7	40	R	+	—	+	++	Severe Burning sensation forearm
8	30	L	+	—	—	—	Severe Choking sensation
9	35	L	—	+	—	+	Tingling in forearm
12	40	L	+	—	+	—	Severe Forearm numb and as if pulled up
15	40	R	+	—	+	—	Severe, as if arm crushed in a vice
16	30	L	+	—	—	++	Severe, as if arm pulled up
17	40	R	+	+	—	—	Severe Fingers numb
18	10	L	—	—	—	—	None
18	40	L	+	—	+	—	Pricking sensation
18	80	R	+	—	+	+	Severe, like arm cut off

and II and summarized in the Figure These results show that a flexion response occurred in an almost equal number of cases in each group The flexion response was confined to the fingers and, although involuntary, could

usually be controlled by the patient, who was able to extend the fingers and counteract it. Where the contraction occurred in patients with myasthenia gravis it did not differ from that seen in the normal subjects and did not resemble in extent or intensity the striking response described by Lanari (1937) and Harvey and Lilienthal (1941). Indeed, the nearest approach to this was seen in two of the normal subjects (Cases 21 and 32). Signs of excess acetylcholine did not occur in every normal subject, but the loss of power in



Diagrammatic summary of the nicotine effects observed after the intra-brachial injection of acetylcholine in 13 normal subjects and 12 patients with myasthenia gravis

the hand was more frequent in that group (see Figure). The paresis was partial and persisted for one to three minutes. In a number of cases (see Figure) the flexion response was followed by loss of power in the hand grip. This suggests that a concentration of acetylcholine sufficient to produce stimulation was followed by a greater concentration with resultant depression. The muscarine effects observed after the intra-arterial injection of acetylcholine are shown in Table III. In order to assess the varying degrees of flush and sweating a system of symbols was devised whereby a definite effect is indicated by (+), a pronounced effect by (++) and a very marked effect by (+++). It will be seen that the distribution and intensity of these effects varied considerably from case to case in each group. The onset of the flush usually occurred within two to five seconds and spread from the forearm to the wrists and fingers. In some instances the flush was preceded by pallor of the fingers and in these subjects the appearance of the flush was delayed for as much as 60 sec. Where this vasoconstriction of the fingers was observed it was usually, but not always, associated with sweating of the palmar surface of the hand. The flush disappeared gradually and in some cases had completely disappeared after six minutes, in other subjects, however, it was still present after 20 min. The time of appearance and duration of sweating was as varied as was the vasodilatation, and no correlation was observed between

Results

The nicotine effects seen in the normal subjects and in the patients with myasthenia gravis after the injection of acetylcholine are recorded in Tables I

TABLE III

The Muscarine Effects seen after the Injection of Acetylcholine into the Brachial Artery of Normal Subjects and Patients with Myasthenia Gravis

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21	40	R	+	+	—	+	Cried out, forearm and fingers numb
22	40	L	—	+	—	+	None
23	40	R	+	—	—	—	Tingling as if fingers and wrists were pulled up
24	40	R	+	—	—	—	Tingling and slight pain in fingers
25	40	R	+	+	—	+	Severe, 'like red hot bar', as if arm pulled up
26	40	L	+	—	+	+	None
27	40	R	+	+	+	+++	None, arm felt dead
29	40	L	+	+	+	+	Pins and needles
30	40	R	+	+	+	+	Severe, like hand cut off
31	40	R	+	+	+	+	None
32	40	L	+++	+++	+++	+++	Moderate in forearm and back of hand
28	40	R	+	+	+	+	None
Patients with myasthenia gravis							
1	40	R	+	—	—	++	Severe pain forearm Choking sensation
3	40	L	++	—	+	++	None, as if wrist drawn up
4	10	L	+	+	+	++	Moderate in forearm and fingers
4	80	L	+++	++	+++	+++	Severe pain, fingers and wrists, as if wrist pulled up
6	40	L	+	+	+	+	None
7	40	R	+	—	+	++	Severe Burning sensation forearm
8	30	L	+	—	—	—	Severe Choking sensation
9	35	L	—	+	—	+	Tingling in forearm
12	40	L	+	—	+	—	Severe Forearm numb and as if pulled up
15	40	R	+	—	+	—	Severe, as if arm crushed in a vice
16	30	L	+	—	—	++	Severe, as if arm pulled up
17	40	R	+	+	—	—	Severe Fingers numb
18	10	L	—	—	—	—	None
18	40	L	+	—	+	—	Pricking sensation
18	80	R	+	—	+	+	Severe, like arm cut off

and II and summarized in the Figure. These results show that a flexion response occurred in an almost equal number of cases in each group. The flexion response was confined to the fingers and, although involuntary, could

always rapid, the solution of acetylcholine being immediately and rapidly injected into the artery. The variability in the muscarine effects is most easily explained by assuming that the distribution of the injected acetylcholine to the skin structures varied from case to case. If this assumption is justified it is reasonable to suppose that the distribution of the acetylcholine to the fore-arm muscles also varied in a similar fashion. These experiments do not fulfil their object in imitating the close-arterial injection technique of animal experiment, since in the latter the distribution of the injected drug is carefully controlled. This factor of variable distribution probably explains the absence of nicotine effects after the intrafemoral injection of acetylcholine in normal subjects (Ellis and Weiss, 1932, Carmichael and Fraser, 1933) and in patients with myasthenia gravis (Fraser, McGeorge, and Murphy, 1937), since the mass of tissue in the thigh is greater than in the arm. In our opinion there is no evidence that the response to injected acetylcholine is a reliable diagnostic test for myasthenia gravis.

Summary

1 The nicotine and muscarine responses to the intrabrachial injection of 10 to 80 mg of acetylcholine have been studied in 13 normal subjects and 12 patients with myasthenia gravis.

2 No striking differences were observed in the nicotine response of normal subjects and of patients with myasthenia gravis. Myasthenic muscle was not found to be peculiarly hypersensitive to injected acetylcholine.

3 The muscarine responses varied from case to case. This variability is discussed in relation to the reliability of this method of testing the sensitivity of muscle to injected acetylcholine in man.

Our thanks are due to Professor E. J. Wayne for access to the cases under his care. We are indebted to Mr. E. Salvin for valuable technical assistance. Part of the expenses of this research were defrayed by a grant from the Medical Research Council to one of us (A. W.), the other (H. B. S.) receives a whole-time personal grant from the same source.

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the flush and sweating. The type of nicotine effect was not related to these variations in muscarinic effects.

Pain was not a constant feature of the injections. Some patients experienced no pain, others only a tingling or numbness of the forearm or fingers. Four normal subjects and 10 patients with myasthenia gravis complained of moderate to severe pain, which was not related to the dose of acetylcholine used. The complaint was made usually within one to five seconds of the injection and lasted for two to three minutes. It was described variously as a burning sensation, a crushing sensation, or a severe numbness as if the hand had been cut off. Several patients in each group described a sensation as if the wrist or arm were pulled up, but this was not related to the actual occurrence of involuntary flexion. Two patients (Cases 1 and 8) complained of a transient choking sensation which occurred about three seconds after the injection, otherwise no general effects were observed to follow the injection. We had an alarming experience with one patient with myasthenia gravis (Case 4) after the injection of 80 mg. of acetylcholine into the left brachial artery. Forty seconds after the injection she complained of feeling very faint, and within 20 sec. she gasped twice very deeply and ceased breathing. She was completely pulseless for 60 sec., and after two rapid deep breaths her face became very pale and sweated profusely. During this time the right forearm was deeply flushed and there was partial flexion of the fingers of the right hand. Two minutes after the injection she was quite conscious and one minute later her pulse and respiration were normal. Although another patient (Case 18) had previously been given a similar dose without incident, we did not feel justified in pursuing the investigation with doses of this magnitude.

Discussion

We have observed no evidence of a striking difference in the sensitivity of normal and of myasthenic muscle to acetylcholine injected intra-arterially, nor have we been able to demonstrate that myasthenic muscle is peculiarly hypersensitive to acetylcholine. This is in agreement with the recent observations of Acheson (1944). It might be argued that the reaction of the myasthenic patient would depend on whether the arm injected was particularly affected by the disease at the time of the test. In only two patients (Cases 7 and 9) was the arm unaffected, neither of whom showed any nicotine effects. This, however, does not throw any light on the difference in the response of all the other patients whose arms were affected. There is no evidence from our experiments that the threshold to acetylcholine is raised in myasthenia gravis, except perhaps that the loss of power, which might be attributed to a depressant level of acetylcholine, was seen more frequently in normal subjects than in patients with myasthenia gravis. Since we carefully followed the technique of Lanari (1937) and Harvey, Lilienthal, and Talbot (1941) we find it difficult to explain the differences in the results obtained by these workers and those recorded by us. One possible point of variation may be in the rate of injection, which, in our experiments was

THE CRYPTOGENIC ACQUIRED HAEMOLYTIC ANAEMIAS¹

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RECENT comment (Haemolytic Anaemias, 1940, Haemolytic Anaemia, 1941) emphasizes the unsatisfactory classification of the acquired haemolytic anaemias, and indicates the need for more clinical work and follow-up studies. In addition to the acquired haemolytic anaemias which may be associated with a great variety of diseases and recognized haemolytic poisons, there is a heterogeneous group which is conveniently called cryptogenic or primary. Although heterogeneous, it includes more or less typical syndromes such as the paroxysmal haemoglobinurias, Lederer's anaemia, and acquired haemolytic spherocytic jaundice, most cases, however, follow no common pattern. The main features of the group are a confusing terminology, an unknown aetiology, an obscure prognosis, an unpredictable response to splenectomy, a liability to transient benefits and stormy reactions from blood-transfusion, an absence of response to any other known haemopoietic aid, and a complete lack of satisfactory pathological basis. The outstanding feature is acquired anaemia attributed to increased blood destruction, typically accompanied by evidence of increased blood formation. The purpose of the present paper is to report and discuss 18 cases of cryptogenic acquired haemolytic anaemia from the records of the Anaemia Clinic and medical wards of the Radcliffe Infirmary. These cases are summarized and arranged for convenience of discussion into three main categories—miscellaneous, acquired haemolytic spherocytic jaundice, and haemolytic anaemia with paroxysmal haemoglobinuria. Additional data are given in the Table.

Miscellaneous

Macrocytic Eight cases with a mean corpuscular diameter greater than $7.71\ \mu$, or a mean corpuscular volume more than $96\ c\mu$.

Normocytic Four cases with a mean corpuscular diameter between 6.78 and $7.71\ \mu$, or a mean corpuscular volume between 75 and $96\ c\mu$.

Red cell size unknown Two cases in which the mean corpuscular diameter and mean corpuscular volume were not available.

Case Summaries

Macrocytic

Case 1 R P, a youth aged 15 years, had two observed haemolytic episodes, both were brief and acute. With the first episode there was jaundice,

¹ Received March 31, 1947.

Normocytic

Case 9 A B, a woman aged 57 years Chronic rheumatism Severe chronic haemolytic anaemia, achlorhydria, abdominal colic, and diarrhoea After splenectomy, gradual but complete remission, punctuated in the early stages by severe haemolytic crises

Case 10 M B, a woman aged 39 years Insidious onset of anaemia, slight jaundice, sore smooth tongue No achlorhydria Red cells showed markedly increased saline and mechanical fragility Gradual spontaneous remission, so far maintained for one and a half years

Case 11 L W, a woman aged 68 years Two adult siblings died from anaemia Slowly progressive anaemia (mean corpuscular diameter 6.9μ) with persistent reticulocytosis and jaundice No response to liver Gastric secretion not examined Death two years after onset

Case 12 L S, a man aged 38 years Chronic mild Raynaud's syndrome Onset of haemolytic anaemia associated with upper respiratory infection, increase in severity of Raynaud's syndrome, high titre of cold agglutinin, and raised serum-globulin Subsequent remission of anaemia, but persistence of reticulocytes, cold agglutinin, raised globulin, and Raynaud's syndrome one year after onset

Red cell size unknown

Case 13 P H, a female child aged 2 years 8 months A week after a cold, sudden onset of anaemia, jaundice, fever, and haemoglobinuria Sustained with blood transfusions, but no dramatic response Recovery six weeks after onset

Case 14 K H, a male child aged 7 months Active rickets Diarrhoea for two weeks, then severe haemolytic anaemia Sustained with blood transfusions, but no dramatic response Recovery two months after onset

Diagnosis In all cases the diagnosis was made because of anaemia, jaundice, and persistent reticulocytosis with a falling or unchanging level of haemoglobin Jaundice was always acholuric except in Cases 2, 5, and 8 In Case 2 the urine contained bile during the first three weeks, there was subsequent acholuria despite raised serum-bilirubin In Case 5 the urine contained bile throughout the period of observation, when there was biochemical evidence of diminished liver function In Case 8 there was a transient episode of deep jaundice and choluria, over two years after the onset of haemolytic anaemia It is recognized that haemolysis is a symptom, not a disease, and that the inclusion only of cases in which haemolysis is an outstanding feature is justifiable solely on the grounds of convenience Haemolysis may be outstanding only because of the lack of recognition of other conspicuous features Pepper (1938) has recently reminded us that this was formerly the case in pernicious anaemia, when he wrote, 'One does not have to go very far back in memory to reach the days when pernicious anaemia was defined as an haemolytic anaemia with abnormal red cell formation, and I can well remember hearing discussions as to whether a patient with pernicious anaemia exhibited sufficient evidence of haemolysis to justify removing the spleen'

meningismus, and transient coma. With the second there was pleural effusion and haemoglobinuria. During both episodes there was neutrophil leucopenia. Two and a half years later he developed classical Wilson's disease (hepato-lenticular degeneration).

Case 2 J S, a man aged 46 years. Rapid onset of anaemia, fever, jaundice, and bilirubinuria. Palpable liver and spleen. Radiological consolidation in lung. Apparent complete recovery with normal haemoglobin five months after onset. Subsequent haemoglobin normal, despite persistent reticulocytosis (4 per cent) two and a half years later, when spleen was impalpable, liver palpable, and liver function normal.

Case 3 E T, a woman aged 48 years. Insidious onset of severe anaemia and neutrophil leucopenia. Splenectomy six months later, with immediate dramatic response, haemoglobin rising to 90 per cent within three months. Gross liver dysfunction developed one and a half years after splenectomy, with oedema, ascites, pigmentation, and marked hepatomegaly. Gradual recovery after a few months. Five years after splenectomy, patient felt well, but had slight residual liver dysfunction.

Case 4 E R, a man aged 49 years. Insidious onset of diarrhoea, fatigue, smooth tongue, and anaemia. Jaundice after one year. No steatorrhoea. Slight biochemical dysfunction of liver, and neutrophil leucopenia. Immediate dramatic response to splenectomy, three months later, haemoglobin 80 per cent, reticulocytes 0.1 per cent, recurrence of neutropenia. Seven months after splenectomy, haemoglobin 100 per cent, reticulocytes 6 per cent, enlarged liver, followed in a few months by gross liver failure (haemoglobin 112 per cent, neutrophils 11,180 per c mm, reticulocytes 3.5 per cent), the patient dying a few days later.

Case 5 G W, a man aged 41 years. Insidious onset of anaemia and jaundice. Diminished liver function. Early haematuria, attributable to renal calculi and congenital hydronephrosis. Fleeting benefit from blood transfusions and no relief from splenectomy. Death from anaemia six months after onset.

Case 6 P R, a woman aged 31 years. Chronic malnutrition. Insidious onset of anaemia, cough, and pleurisy. Radiological lung opacity of undetermined nature. Early transient response of anaemia to full diet with iron, marmite, and vitamin C. Later, reticulocytosis of 37 per cent (highest recorded) three days after 12 c.c. of B D H liver extract intramuscularly, without corresponding rise in haemoglobin. Histamine-fast achlorhydria. No benefit from splenectomy, haemolytic anaemia still present (haemoglobin 34 per cent) two years later.

Case 7 D P, a woman aged 22 years. Recurrent haemolytic crises every few months with rapid spontaneous recovery. No apparent precipitating cause. Abnormal plasma albumin-globulin ratio.

Case 8 D S, a male child aged 6 months. Diarrhoea since birth. Marasmus. Subacute onset of anaemia. Dramatic and prolonged response to small blood transfusions, but eventual recurrences. Splenectomy, three years after onset, with doubtful benefit. Reticulocytes before splenectomy were usually 3 to 4 per cent, and haemoglobin 26 to 60 per cent. After splenectomy, during the subsequent two years of observation, reticulocytes 10 to 20 per cent, haemoglobin 60 to 70 per cent.

disease), no earlier liver disease having been observed. The second (Case 5) showed concurrent liver damage. The third and fourth (Cases 3 and 4) developed gross liver damage after having been cured of the anaemia.

In Case 1, the earliest clinical evidence of possible cerebral damage, at the time apparently very transient, occurred just before the first haemolytic episode, at the age of 15 years. There was no family history of relevant disease and no history of erythroblastosis foetalis. There were two brothers, one of whom died aged four months of whooping cough, the other was killed in a car accident when aged 10 years. When Wilson's disease appeared, two and a half years after the first haemolytic episode, it was described as classical in type, and Kayser-Fleischer rings of corneal pigmentation were observed. The evidence of eventual liver damage is presumptive and is based on the subsequent development of Wilson's disease. Liver function was not estimated during the haemolytic episodes. There appears to be no previous reference in the literature to Wilson's disease as a sequel to acquired haemolytic anaemia. The sequel may have been a chance one and its rarity forms an interesting contrast to the frequency of chronic nervous disease and the known occurrence of juvenile cirrhosis as a result of erythroblastosis foetalis. Attacks of jaundice and symptoms referable to acute hepatitis are, however, known to occur sometimes in Wilson's disease before the onset of the nervous symptoms (Walshe, Collier, and Adie, 1937). In the present case jaundice was much more evident than the slight anaemia, and the reticulocyte count was a useful indication of the factor of haemolysis. There seems to be a possibility that the attacks of jaundice known sometimes to precede Wilson's disease are not invariably the result of acute hepatitis. Wilson's disease, although rare, is often familial and it would be of particular interest in such families to observe the reticulocyte and haemoglobin levels during any attacks of jaundice to ascertain if haemolysis is ever a factor in such cases.

There are grounds for considering in Cases 3 and 4 that splenectomy, curing the anaemia, contributed to the subsequent liver failure. Additional details of these cases are as follows.

Case 3 Onset of anaemia in 1941. One month before splenectomy the liver was palpable and the spleen enlarged. Liver function tests showed total plasma-proteins 5.8 gm per 100 c.c., phosphatase 7 units, 87 per cent excretion of sodium benzoate as hippuric acid within four hours, serum-bilirubin 3 mg per 100 c.c., and very slightly abnormal elevation of glucose and lactulose curves. Wassermann and Kahn reactions positive. Consistent neutrophil leucopenia before splenectomy, between 1,144 and 1,680 per c.mm., with maximum total leucocytes of 3,600 per c.mm. Typical blood picture, haemoglobin 40 per cent, red cells 2,000,000 per c.mm., reticulocytes 10 per cent, mean corpuscular diameter 7.82μ , mean corpuscular volume $90.5 \text{ c}\mu$. Splenectomy, six months after the onset, showed a liver which appeared normal. Nitrogen balance was negative (approx. 1.0 gm per diem) before, and for the two-week period after, splenectomy. The operation was followed at once by a permanent return of the leucocytes to normal levels. Pre-operative transfusions had raised the haemoglobin to 72 per cent and this level, without subsequent transfusions, rose above 90 per cent within three months,

Preceding diseases The only notable preceding disease was tuberculosis. There was a history of remote tuberculous infection in five of the 11 adult cases of the series. In none was there evidence of a recurrence of activity with the onset of anaemia, and in all the period of preceding quiescence was at least five years. The manifestations of tuberculosis were cervical adenitis (Cases 9 and 10), pleurisy (Case 5), and pulmonary tuberculosis (Cases 3 and 11). This incidence of quiescent tuberculosis is remarkably high, although the significance of the finding can be decided only from further cases. The association of active tuberculosis with haemolytic anaemia was observed by Widal, Abramí, and Brulé (1907) and Chauffard (1914), who regarded hereditary syphilis and tuberculosis as the most common associated factors. More recent literature refers to the association with tuberculosis of the spleen (Engelbreth-Holm, 1938) and the spleen and lymph nodes (Thompson, 1936).

Diseases associated with the onset A presumptive respiratory infection was related to the onset in four cases. In one (Case 13), an infant, there was a cold for the previous week. In one (Case 2) there was radiologically a patch of pneumonitis, with fever and dark urine. In Case 6 there was an insidious onset of anaemia and cough, six months later, on first examination, there was low-grade fever, cough, and a pleural rub. Radiologically there was consolidation in the right lung and a pleural effusion on the same side. The consolidation and the effusion cleared slowly, the sputum gave no clue to the nature of the lesion. In the fourth patient (Case 12), symptomless anaemia and jaundice first appeared after two heavy colds.

In Case 6 the serum contained an autohaemolysin active at 37°C, and in Case 12 there was a high titre of cold agglutinin, active in a thermal range from 4 to 34°C. These were the only cases in the whole series in which could be demonstrated substances in the serum of an immune-body type which were active *in vitro* against the patient's red cells. The findings suggest the possibility that an antigen associated with infection may at times stimulate the production of an antibody active against red blood cells. It is not suggested, however, that in Case 6 the autohaemolysin played any active part in the production of excessive haemolysis within the body. The very fact that surplus haemolysin and unhaemolysed red cells were available for an *in vitro* demonstration of haemolysis at body temperature is good evidence of the *in vivo* inadequacy of the haemolysin.

In two cases there was evidence of malnutrition. In one (Case 6) the habitual diet had been chiefly white bread and tea. In Case 4 the diet was normal, but for a year before jaundice appeared there was diarrhoea and wasting.

In one patient (Case 1) the first haemolytic episode was associated with a cerebral disturbance of unknown nature, an association of particular interest because the patient developed hepato-lenticular degeneration two and a half years later.

Liver function Four patients had a related liver dysfunction. The first (Case 1) had the late sequel of hepato-lenticular degeneration (Wilson's

Additional Data

Excess urinary urobilin	Choluria	Serum bilirubin (mg per 100 c c)	Mean corpuscular saline fragility (gm. NaCl per 100 c c)	Increased acid fragility	Increased carbon dioxide fragility	Donath Landsteiner test	Autohaemolysis (Dacie)	Enlarged spleen	Enlarged liver	Remarks	Outcome
No	No	0.6	0.35	No	No	Neg	No	Yes	No	Data during remission	Wilson's disease
Yes	Early only	2.2	0.41	"	"	"	"	"	Yes	Data during disease	—
	No							No	"	Data after sustained remission	Good
No	"	3.0	0.38	"	"	"	—	Yes	"	Data before splenectomy	—
		0.2								Data 1½ years after splenectomy	Ultimately good
Yes	"	1.8	—	—	—	—	—	"	No	Data before splenectomy	—
	Yes	1.3								Data 1 year after splenectomy	Died
"	"	4.0	0.41	No	No	Neg	—	"	Yes	—	"
—	—	1.1	0.44	Yes	"	"	Yes	"	No	—	Doubtful
No	No	0.7	0.38	—	—	"	No	No	"	—	"
Yes	"	2.2	0.38	—	—	—	—	Yes	Yes	Data 2½ years after onset	—
		1.0								Data 3 years after onset, before splenectomy	Doubtful
—	—	—	—	—	—	—	—	"	"	Van den Bergh indirect positive (3 units) Red-cell fragility began at 0.54 gm per 100 c c saline	Good
Yes	No	1.9	0.46	—	—	Neg	No	"	No	Marked increase in mechanical fragility	"
—	—	—	—	—	—	—	—	"	—	—	Died
Yes	No	4.2	0.46	—	—	—	—	"	—	Powerful cold haemagglutinin in serum	Doubtful
Yes	—	4.0	0.39	—	—	—	—	No	No	—	Good
—	—	—	0.36	—	—	—	—	—	—	—	"
—	—	6.0	0.46	—	—	—	—	Yes	No	Marked spherocytosis, Coombs's test positive	Doubtful
—	—	2.2	0.36	—	—	—	—	"	"	Nocturnal haemoglobinuria	Fairly good
—	—	0.2	0.41	Yes	Yes	Neg	—	—	—	Nocturnal haemoglobinuria	Poor
—	—	1.0	0.38	—	—	"	—	No	No	Data 4 years after onset	"
										Data 3 years after onset	"

Donath Landsteiner reaction, *in vitro* haemolysis when blood is warmed to 37° C after chilling, Beck (1938)

Mean corpuscular fragility, Dacie and Vaughan (1938)

The data, unless otherwise stated, are from the established disease and before splenectomy

Case	Age at onset (years)	Sternal marrow	Mean corpuscular volume (c.μ)	Mean corpuscular diameter (μ)	Coefficient of variation (%)	Macrocytosis (%)	Reticulocytosis (%)	Hemoglobin (%)	Neutrophils (per c.mm.)	Platelets (thousands per c.mm.)	Histamine-fast achlorhydria	Plasma albumin (gm per 100 c.c.)	Total plasma protein (gm per 100 c.c.)	
1	15	Normoblastic	110	8.03	6.2	63.2	1.2 to 3.6	78	1,848	110	No	—	—	Ult d
2	46	"	—	7.90	6.8	59	4.2	74	2,300	240	"	—	—	
							4.6	98				5.0	7.5	Non
3	48	"	95	7.83	8.0	33.2	9.2	42	1,144	167	"	—	5.8	Pos d
			92.5					110				3.0	6.2	Gro is
4	49	Normoblastic, a few megakaryoblasts	100	—	—	—	7.0	30	700	130	Yes	4.2	6.25	Dim
							3.5	112	11,180			2.05	6.41	Gro is
5	41	Normoblastic	—	8.18	8.6	51.2	10.0	30	1,900	153	No	4.0	5.6	Non
6	31	"	105	8.66	9.6	74.8	14.0	38	3,900	100	Yes	3.5	5.95	
7	22	"	—	8.66	8.9	58.8	26	50	7,480	254	—	4.8	6.25	Non
8	6/12	Megaloblastic	—	7.78	13.8	14	9.2	55	7,740	339	No	4.45	7.8	
		Normoblastic					4	60	4,400			4.4	7.5	
9	57	—	—	7.64	—	—	20 to 40	48	3,900	160	"	—	—	
10	39	Normoblastic	—	7.64	8.5	13.8	10.6	78	4,752	346	"	3.9	6.05	Non
11	08	—	—	6.9	—	—	6.0	50	4,355	++	—	—	—	
12	38	—	83	—	—	—	7.8	82	6,624	—	—	4.6	7.95	
13	2½	Normoblastic, tending to macro normoblastic	—	—	—	—	10.0	40	13,200	190	No	—	—	
14	7/12	—	—	—	—	—	9.0	30	11,857	163	—	—	—	
15	69	Normoblastic	109	—	—	—	52.0 to 5	30	900	20	No	4.0	6.5	
16	24	—	125	8.85	9.1	71.4	15.0	50	3,822	385	"	5.37	7.12	Non
17	30	—	—	7.99	5.5	59.2	25.4	64	3,402	185	—	4.3	6.95	
18	41	Normoblastic	100	8.2	8.3	53.8	6.2	44	1,748	210	Yes	3.85	6.7	T

Methods

Mean corpuscular diameter, coefficient of variation, and macrocytosis, Price-Jones (1933)
Mean corpuscular volume, by haematocrit method, Wintrobe (1933)
Increased acid fragility and increased carbon dioxide fragility, Ham (1939)
Autohaemolysis, *in vitro* haemolysis in blood clot kept at 37° C., Dacie and Richardson (1938)

c mm, reticulocytes 3.5 per cent, total leucocytes 13,000 per c mm, neutrophils 11,180 per c mm. The patient died a few days later.

Post-mortem examination showed osteoporosis of the ribs, sternum, and vertebrae, all of which contained red marrow. The femur showed red marrow extending along the whole length of the shaft. There was extensive bronchopneumonia. The liver weighed 3,768 gm, its cut surface showed jaundice, fatty change, and areas of congestion. Microscopically the liver showed widespread areas of necrosis and haemorrhage, in the sinusoids there was an intense infiltration with neutrophils and mononuclear cells, surviving liver cells showed fatty and pigmentary change. There was no evidence of hepatic cirrhosis.

The sequence of events in Cases 3 and 4, the appearance of the liver at the time of splenectomy, and the relatively slight pre-splenectomy disturbance of liver function, suggest that the condition was not merely increased destruction of red blood-cells occurring during the course of an established cirrhosis, such as may occur in atrophic cirrhosis (Watson, 1937) or Hanot's hypertrophic cirrhosis (Eppinger, 1920). Fatty change and granular degeneration are known to occur in some cases of haemolytic anaemia (Rich, 1930, Farrar, Burnett, and Steigman, 1940), disturbances which could have contributed to the liver damage, but which in themselves do not explain why severe liver damage appeared only when the haemolytic anaemia had been cured. That severe liver disease followed the two most successful responses to splenectomy is hardly a paradox which occurred by chance. Although the primary cause of the liver damage in these cases is not known, there was a possible contributory damaging process which is consistent with the sequence of events and merits consideration because of the known ill effects of protein malnutrition on liver disease. The details of this subsidiary process are as follows.

There was evidence of excessive loss of bodily protein before splenectomy and the protein intake was subject to the dietary restrictions of the war period. In Case 3 there was a negative nitrogen balance and a total plasma-protein of 5.8 gm per 100 c.c. In Case 4 there was chronic diarrhoea, loss of weight, and a plasma-albumin falling from 4.2 to 3.1 gm per 100 c.c. During this period the spleen, presumably the major site of the excessive haemolysis, delivered the products of haemolysis to the liver as a protein supplement via the splenic vein—a priority protein supply cut off by splenectomy. Surgical operations in themselves are known to increase protein destruction (Cuthbertson, 1945) and splenectomy doubtless produced this additional effect. The successful cure of the anaemia by splenectomy caused a still further depletion of the protein stores of the body because of the demands made by the additional synthesis of haemoglobin (Heath and Taylor, 1936, Holmes, 1945) as the haemoglobin level rose to normal.

In terms of protein supplies available to the liver, it therefore seems probable that in these two cases splenectomy was one of several factors causing depletion, and that the depletion was greater because the splenectomy was successful. Until the relative importance of this effect of splenectomy can be assessed by more extensive observations, it seems reasonable to suggest

remaining above it thereafter. The reticulocytes, reduced by pre-operative transfusions to 1.6 per cent, rose to 3.2 per cent on the fourth day and subsequently remained at or below 2.0 per cent. At the eighteenth month after splenectomy the patient felt very well, but the liver was greatly enlarged, and six months later she developed oedema, ascites, a spider naevus on the face, cyanosis, dyspnoea, and skin pigmentation. Plasma-albumin 3.0 gm per 100 c.c., plasma-globulin 3.2 gm per 100 c.c., Takata-ara reaction positive, phosphatase 60 units, bilirubin 0.2 mg per 100 c.c., haemoglobin 110 per cent, mean corpuscular volume 92.5 μ . The symptoms of severe liver dysfunction persisted for several months, then gradually regressed. Five years after splenectomy (the most recent observation) the patient felt very well and lived a normal life, but there was slight residual liver dysfunction (albumin 3.7 gm per 100 c.c., globulin 3.36 gm per 100 c.c., phosphatase 4 units, Takata-ara reaction weak-positive). The Wassermann reaction became negative soon after splenectomy, positive three months later, and negative after the following three months. The positive reactions were not attributed to syphilis.

Case 4 The patient was first examined in 1942 after having had diarrhoea, exertional dyspnoea, loss of weight, increasing pallor and fatigue for the previous year, and jaundice for the previous month. At this stage, one year after the onset, the spleen was moderately enlarged, the liver not palpable. Plasma-albumin 4.2 gm per 100 c.c., plasma-globulin 2.0 gm per 100 c.c., phosphatase 10 units, serum-bilirubin 2.2 mg per 100 c.c., total leucocytes 700 per c.mm., red cells 1,500,000 per c.mm., haemoglobin 30 per cent, reticulocytes 7.5 per cent, mean corpuscular volume 92 μ . Pre-splenectomy neutrophil counts were consistently below 1,000 per c.mm. No steatorrhoea, and normal proportion of split faecal fats. Fifteen months after the onset the blood picture was essentially unchanged. Plasma-albumin 3.1 gm per 100 c.c., plasma-globulin 4.1 gm per 100 c.c., hippuric acid excretion 90 per cent within four hours, Takata-ara reaction positive, serum-cholesterol 80 mg per 100 c.c., plasma-bilirubin 1.8 mg per 100 c.c., sucrose tolerance curve normal. Splenectomy was performed 16 months after the onset. Neutrophils rose on the same day to 5,806 per c.mm., but fell three months later to 450 per c.mm., subsequently remaining below 1,000 per c.mm. until the onset of terminal liver failure one year after splenectomy. Haemoglobin, raised to 50 per cent by pre-operative transfusion, rose without further transfusion to 80 per cent three months after splenectomy, reticulocytes falling to 0.1 per cent. The patient felt very well and returned to work a month later. Seven months after splenectomy he had low-grade fever and upper abdominal pains. Laparotomy then showed an enlarged smooth liver which appeared congested. Cholecystectomy was done, no gall stones were present. A month later the results of liver function tests were essentially the same as those one month before splenectomy. Haemoglobin 84 per cent, reticulocytes 6.8 per cent, neutrophils 910 per c.mm., bilirubin 2.0 mg per 100 c.c. Nine months after splenectomy the liver became much enlarged, haemoglobin 100 per cent, reticulocytes 4.9 per cent. One year after splenectomy the patient was readmitted to hospital. He was very emaciated, jaundiced, and oedematous. The urine contained bile, the liver edge reached the level of the umbilicus. Blood-urea 51 mg per 100 c.c., phosphatase 11 units, plasma-bilirubin 13 mg per 100 c.c., plasma-albumin 2.05 gm per 100 c.c., plasma-globulin 4.36 gm per 100 c.c., Takata-ara reaction positive, cholesterol 80 mg per 100 c.c., haemoglobin 112 per cent, red cell 5,100,000 per

Wilson's disease Case 2 recovered from the anaemia after five months, but in 1943, two and a half years after the onset, there was still a persistent reticulocytosis of about 4 per cent In Case 7 the course was marked by prolonged remissions and the outcome is not yet clear Case 11 died two years after the onset at the age of 70 years In Case 12 there is now, one year after the onset, no anaemia, but a reticulocytosis (4 per cent) and serological abnormalities are still present Case 10 has had a complete remission, sustained so far for one and a half years Splenectomy, which was reserved for the six more severe or chronic cases, unequivocally cured the anaemia in two patients (Cases 3 and 4), one of whom later died of liver failure Splenectomy probably cured a third patient (Case 9) The fourth (Case 8) survived the operation without apparent benefit and ultimately recovered The fifth (Case 6) remains unchanged two years later, and the sixth (Case 5) died without temporary alleviation In seven out of the eight cases without splenectomy the anaemia recovered, but of these seven only three are completely well

Transfusions The general policy followed was to give transfusions to all cases except those with only slight anaemia or those recovering spontaneously The transfusions were of stored whole blood or packed red cells prepared from the blood bank, and they were almost always from the same blood group as the patient Occasionally compatible Group O blood was given to patients of other blood groups Cross-matching was always carried out, in the more recent cases a tube-incubation method was usually employed (Wintrobe, 1942) All transfusions were given slowly by intravenous drip Of 11 cases transfused, three had single transfusions and the remainder had from two to 10 Minor febrile reactions were not uncommon and appeared harmless Alarming reactions in the form of severe rigors occurred in four patients In three of these (Cases 2, 5, and 9) the course of the disease was febrile In the fourth (Case 6) a severe reaction occurred only after the second of 10 transfusions, this reaction proved to have been the result of Rh incompatibility, subsequent transfusions of Rh-negative blood produced no reactions The good effects of transfusions were most evident in the following ways the production of prolonged remissions (Case 8), the maintenance of life until the appearance of a natural remission (Cases 13 and 14), pre-operatively to diminish the risks of splenectomy (Cases 3, 4, 5, 6, 8, and 9), and for the avoidance of chronic invalidism (Case 6)

Acute haemolytic anaemia (Lederer's anaemia) Although there is a gradual merging between cases of acute, subacute, and chronic haemolytic anaemia (Dameshek and Schwartz, 1938), the separate consideration of acute cases is merited because of the classical sharp febrile onset, the rapidly progressive anaemia, the short self-limited course, and the dramatic effect which frequently follows blood transfusion, without which the prognosis is grave (Wintrobe, 1942) Three patients (Cases 8, 13, and 14) in the present series showed some of the features of Lederer's anaemia In two, blood transfusion appeared to sustain rather than cure, in the third, dramatic response to

that in patients with a low plasma-albumin or suspected liver damage, splenectomy may be a particular hazard, and that the hazard would be diminished by a high protein diet and blood-transfusion for a prolonged period before and after splenectomy

Neutrophil leucopenia Four of the total of 14 cases showed in the earliest period of observation a neutrophil leucocyte figure consistently below 2,000 per c mm. These four (Cases 1, 3, 4, and 5) all had related liver dysfunction and have been discussed above. In Case 1, only during a remission between the two observed haemolytic episodes was there a single total leucocyte count of 7,000 per c mm, no differential leucocyte count was available. Neutropenia was not present at any time in the 10 cases which showed no evidence of liver dysfunction. In retrospect, neutropenia was the only early and consistent herald of liver dysfunction. Its possible value as an indication for serial observations of liver function can be decided only when more data become available. Splenectomy was performed in three cases with neutropenia (Cases 3, 4, and 5). In all three the neutrophils rose to normal within a day or two. In Case 5 the count remained high during the remaining three weeks of life, although haemolysis was unabated. In Case 3 the neutropenia did not recur despite the subsequent severe liver dysfunction. In Case 4 neutropenia recurred after three months, but with the onset of liver failure the figure rose to 11,180 per c mm. Splenectomy was performed in three cases without neutropenia (Cases 6, 8, and 9). In all three the neutrophil count rose, yet in two (Cases 6 and 8) there was no evidence that the operation was beneficial and in Case 9 it was of doubtful benefit. A post-splenectomy rise in neutrophils was not therefore of prognostic value.

Splenectomy The range of recent opinions about the value of splenectomy in acquired haemolytic anaemia is best illustrated by the following extracts from the literature. 'In the macrocytic haemolytic anaemias it [splenectomy] offers the only chance of a successful outcome' (Davidson and Fullerton, 1938). 'It may slightly modify the course [in macrocytic types] but it does not cure' (Dyke and Young, 1938). 'It has been successful [in acute haemolytic anaemia] as a last resort in cases not responding to transfusion' (Dameshek and Schwartz, 1940). 'Splenectomy is not indicated except in typical spherocytic jaundice' (Thompson, 1936). 'Splenectomy gives results that are analogous with those obtained in the hereditary disease' (Meulengracht, 1938). One source of difficulty in assessing the value of splenectomy in the present series was the extremely variable natural course of the haemolytic process. For this reason, recovery of health after splenectomy has not been regarded *per se* as evidence of anything more than ability to survive the operation. Splenectomy was regarded as curative only when the good effect on the anaemia was rapid, progressive, and sustained. In the present series of 14 cases, eight retained their spleens (Cases 1, 2, 7, 10, 11, 12, 13, and 14). Two were acute cases occurring in infants (Cases 13 and 14) who recovered within two months of onset, being sustained until then by blood transfusions. Of the six chronic cases, Case 1 recovered from anaemia but developed

later became normoblastic, achlorhydria was not present. When macrocytic anaemia is associated with normoblastic marrow the macrocytosis is sometimes ascribed to intense activity of the bone-marrow (Wintrobe, 1942). In the present series the lack of correlation between macrocytosis and reticulocytes (see Table) suggests either a more complex cause or that the level of persistent reticulocytosis is not a reliable indicator of bone-marrow activity. In four of the present series, liver function was either diminished (Cases 3, 4, and 5) or probably diminished (Case 1), and this may have been a contributing factor, in view of the known association of macrocytic anaemia with liver disease (Wintrobe, 1942).

Acquired Haemolytic Spherocytic Jaundice

Case 15 B C, a woman aged 69 years. Onset with transient purpura and polyarthritides, then a haemolytic crisis. Subsequent neutropenia and thrombocytopenia. Mean corpuscular fragility 0.46. Consistently marked spherocytosis. Sternal marrow showed active normoblastic erythropoiesis, otherwise essentially normal. Splenectomy followed by haemolytic crisis and later by recurrence of thrombocytopenia and purpura. Haemolytic anaemia still present one year after splenectomy. Post-splenectomy Coombs's test positive.

Case 15 was the only example of acquired haemolytic spherocytic jaundice in the present series. It was also the only case with haemolytic anaemia, neutropenia, and thrombocytopenic purpura, an uncommon syndrome which appears to correspond with that described by Frank (1943) as splenopathic leucopenia and Wiseman and Doan (1942) as primary splenic leucopenia.

As a result of recent studies the probable haemolytic mechanism in acquired spherocytic jaundice has become clearer. Dameshek and Schwartz (1938) produced spherocytosis and increased saline fragility of red cells in animals by the injection of haemolytic sera. On the basis of this work they have suggested (Dameshek and Schwartz, 1940) that haemolytic spherocytic jaundice is the result, at least in part, of the action of haemolysins which produce spherocytosis, increased fragility, and increased haemolysis. This postulate has received striking support in acquired spherocytic jaundice, although not in the congenital form, by Boorman, Dodd, and Loutit (1946). These workers have shown, by the application of Coombs's anti-human globulin serum test (Coombs, Mourant, and Race, 1946) that immune antibody globulin can be demonstrated on the patient's red cells in acquired spherocytic jaundice. In two of their cases splenectomy produced a symptomatic cure, although Coombs's test indicated that immune antibody was still present on the red cells, spherocytosis and increased fragility also persisted. From these studies it appears probable that the demonstrable sensitization of the red cells by immune antibody in acquired acholuric jaundice is causally related to the spherocytosis, increased fragility, and increased destruction of the red cells. Because spherocytosis and sensitization can persist after splenectomy, there is no reason to attribute the symptomatic

blood transfusion, with apparent cure, was followed by a series of relapses, culminating in a splenectomy which was of doubtful benefit

Case 13 P H, a female child aged 2 years 8 months Acute febrile onset of anaemia after a cold Neutrophils 13,200 per c mm Deep jaundice Haemoglobinuria Spleen and liver not palpable Despite two transfusions of whole blood (total 490 c c), haemoglobin fell to 28 per cent By the seventh day, after the third and last transfusion (250 c c), haemoglobin 50 per cent, reticulocytes 5 per cent Subsequently the reticulocytes varied between 28 and 4 per cent, tending to fall, and the haemoglobin 50 to 56 per cent, until the sixth week, when haemoglobin rose to 72 per cent and reticulocytes fell to 0.5 per cent

Case 14 K H, a male child aged 7 months Acute febrile onset, jaundice, haemoglobinuria, liver and spleen not palpable Haemoglobin 30 per cent, reticulocytes 9 per cent, total leucocytes 33,000 per c mm After two blood-transfusions (total 550 c c), haemoglobin on sixth day was 40 per cent No further transfusions On thirteenth day, haemoglobin 46 per cent, reticulocytes 28 per cent By sixth week, haemoglobin 74 per cent, reticulocytes 1 per cent

Case 8 D S, a male child aged 6 months Marasmus Subacute onset of anaemia, jaundice, low-grade fever Enlarged liver and spleen Haemoglobin 38 per cent, reticulocytes 9 per cent One blood transfusion of 250 c c caused a rise of haemoglobin to 88 per cent, reticulocytes falling to 2.2 per cent Relapse of anaemia six months later, again with dramatic response to transfusion (180 c c) Subsequent relapsing course (haemoglobin 26 to 60 per cent, reticulocytes 3 to 11 per cent) Transfusion for splenectomy raised haemoglobin to 75 per cent Splenectomy performed three years after onset During subsequent two years of observation, haemoglobin remained 60 to 70 per cent, but the reticulocytes, previously never higher than 11 per cent, were subsequently 10 to 15 per cent, and two years after splenectomy were 20 per cent and haemoglobin 70 per cent

Cases 13 and 14 suggest that the lack of dramatic response to transfusion does not necessarily indicate a bad prognosis Conversely, Case 8 suggests that a dramatic response and apparent cure may be followed by recurrences It was difficult to assess the effect of splenectomy on the anaemia in Case 8, because of the varying course before the operation The effect on the haemoglobin level was certainly less evident and more open to doubt than the effect on the reticulocytes, which were regularly sustained at a much higher level after splenectomy If a prolonged rise in reticulocytes can be accepted as a sign of an increased rate of erythropoiesis, then in this patient splenectomy appeared to increase red-cell formation more than it decreased red-cell destruction

Macrocytosis The anaemia was macrocytic in eight of the 12 cases in which the size of the red cells was estimated In six of the eight macrocytic cases the sternal marrow showed active normoblastic erythropoiesis In the seventh (Case 4) the marrow was normoblastic with a few megaloblasts, in this patient there was histamine-fast achlorhydria In the eighth, an infant (Case 8), the marrow was megaloblastic in the early stage of the disease and

because of the occasional curious exacerbating influence of the menstrual cycle in other blood disorders such as thrombocytopenia and neutropenia

Splenectomy Splenectomy in nocturnal haemoglobinuria is usually regarded as ineffective (Scott, Robb-Smith, and Scowen, 1938, Dacie and Firth, 1943) In Case 15 splenectomy was performed two years after the onset because the anaemia and attacks of haemoglobinuria were becoming progressively worse After the operation there was a gradual but progressive improvement It seems probable, therefore, that in this patient splenectomy was of value

Blood-transfusions At the worst, blood-transfusions in nocturnal haemoglobinuria may result in severe haemolytic episodes (Hamburger and Bernstein, 1936) and at the best they may produce remissions (Ham, 1939) Neither extreme was experienced in the present three patients Case 16 had one transfusion, Case 17 had two, and Case 18 had many There were no serious reactions in any, there was benefit to the anaemia in all, and remission in none

Discussion

The frequency of increased haemolysis as a symptom in acquired disease is abundantly illustrated by its occurrence in pernicious anaemia, the allied macrocytic anaemias, leuco-erythroblastic anaemia (Brown, Hayward, Powell, and Witts, 1944), aplastic anaemia (Rhoads, 1939), Hanot's cirrhosis (Eppinger, 1920), and atrophic cirrhosis (Watson, 1937) In the present series of 18 cases it appeared as a symptom in strikingly dissimilar syndromes As a symptom increased haemolysis is as ubiquitous as dermatitis in skin disease, with perhaps as complex a pathology in terms of essential growth factors, dysplasia, varying resistance to normal wear and tear, and exposure to excessive processes of attrition It connotes increased attrition in the haemopoietic system, a tissue of the body which offers unique facilities for observation of its germinal cells, the size and durability of the adult cell mass, the metabolic products, and the serological and biochemical composition of its internal environment It cannot be supposed that the pathological processes which are indicated by increased haemolysis are exclusive to a single tissue of the body or that, when they become known, the pathological principles cannot be applied to disease in other tissues less amenable to observation In the present paper the main purpose has been to report the available data from 18 cases in which there was increased haemolysis of unknown origin The features which have been emphasized are those which might give information about the natural course of the disease processes, the tentative therapeutic approach, and those which seem of possible pathological significance The conclusions are based on facts which are sometimes isolated or selected from cases not necessarily pathologically related

effects of splenectomy in this disease to anything more than removal of a major source of destruction of the sensitized red cells. The implications of this view of the haemolytic mechanism in acquired spherocytic jaundice are of interest because of the associated neutropenia and thrombocytopenia in Case 15. In this patient there were three components which were diminished in the peripheral blood, despite active and essentially normal haemopoiesis. The red-cell component was deficient because of excessive destruction due to sensitization by a globulin of immune antibody type. It seems reasonable to postulate a similar rather than a dissimilar pathological process to account for the deficiency in the other two components, the platelets and the neutrophils.

Haemolytic Anaemia with Paroxysmal Haemoglobinuria

There were three cases of paroxysmal haemoglobinuria associated with chronic macrocytic haemolytic anaemia. In all three the haemoglobinuria was nocturnal (Marchiafava-Micheli syndrome).

Case 16 C S, a woman aged 24 years. Gradual onset of malaise, then influenza and nocturnal haemoglobinuria which was at first intermittent. Colds caused exacerbations of haemoglobinuria. Exacerbations sometimes occurred before menstruation. Splenomegaly. Splenectomy two years after onset. Subsequent gradual relief. Mild symptoms compatible with normal life 10 years after onset.

Case 17 O E, a woman aged 36 years. Onset with transient nocturnal haemoglobinuria after a chill. Recurrence three years later after influenza. Haemoglobinuria worse before menstruation and with colds. Illness still severe nine years after onset.

Case 18 O B, a woman aged 41 years. Gradual onset of exertional dyspnoea and undue fatigue. Nocturnal haemoglobinuria a year later. Haemoglobinuria always intermittent, sometimes provoked by colds. Neutropenia usual. Slow downhill progress three years after onset, the patient needing transfusions every few months.

As the condition is rare and its cause unknown, it may be of interest to stress the factors in the present cases which appeared to influence the course of the disease.

Infections In all three patients colds produced exacerbations or recurrences of nocturnal haemoglobinuria. In Case 15 haemoglobinuria was first associated with influenza, an infection which provoked a recurrence in Case 16. The provocative effects of colds and other intercurrent infections are well known not only in nocturnal haemoglobinuria but also in congenital spherocytic jaundice, in which they can produce haemolytic crises. The relation of respiratory infections to the onset in other patients (Cases 2, 6, 12, and 13) in the present series has already been discussed. In all these disorders, however, the mechanism by which infections act is at present unknown.

Menstruation In two patients (Cases 16 and 17) there were exacerbations of haemoglobinuria before menstruation. The relationship is interesting

haemoglobin Reticulocytosis sometimes persisted after the haemoglobin returned to normal, suggesting that excessive haemolysis may be present without anaemia

Serological abnormalities In one case there was an autohaemolysin active at 37° C, and in one there was a powerful cold agglutinin In a third case the red cells were sensitized by a globulin of immune-body type, in this case there was marked spherocytosis and increased saline fragility

Sequels After symptomatic cure of the anaemia there were the following sequels, each occurring in one case hepato-lenticular degeneration, palpable liver with persistent reticulocytosis, residual liver dysfunction, death from liver failure, abnormal albumin-globulin ratio in plasma, and raised serum-globulin and cold haemagglutinin

I should like to acknowledge my thanks to Dr A M Cooke for the clinical records in Cases 4 and 15, to Dr A H T Robb-Smith and Dr R G Macfarlane for the pathological data in Cases 4, 8, 13, 14, and 15, to Mr J R P. O'Brien for the biochemical data, and to Professor L J Witts for his criticism.

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Conclusions

Natural course This was extremely variable. The illness was usually grave, and sometimes fatal. A sustained remission of the anaemia, not attributable to treatment, can occur even after many months.

Blood-transfusions Transfusions permitted a waiting policy, sustained life, induced remission, prepared for splenectomy, and probably hastened convalescence. Transfusions were reasonably safe, with a tube-incubation method of cross-matching, donor blood of the same group as the patient, slow rate of delivery by the intravenous drip, and regard for the possibility of Rh incompatibility.

Splenectomy The best effect of splenectomy on the anaemia occurred in two patients with neutropenia who later developed gross liver damage. A good effect was probable in two other cases, one a case of nocturnal haemoglobinuria. It has been suggested that successful splenectomy can endanger the protein supplies available to the liver and that this possible hazard can be anticipated. Splenectomy can cure the anaemia, the reticulocytes dropping to normal. It can also cause a sustained rise of reticulocytes to a higher level without curing the anaemia. It can increase the circulating neutrophils, and can provoke a haemolytic crisis.

Treatment As it is not yet possible to predict the effects of splenectomy, it appears reasonable to maintain the patient with blood-transfusions for a period of a few weeks to a few months, a period during which there is opportunity for a remission or, alternatively, preparation for splenectomy when the course is unremitting and severe. There was no evidence that liver therapy was of value, or that iron was indicated except when haemoglobinuria threatened to deplete the iron store of the body.

Infections Tuberculosis, for long quiescent, was a precursor in five of the 11 adult patients in the miscellaneous group. Colds and influenza appeared in some cases to precipitate or to provoke exacerbations of the haemolytic process. In two of these cases there were serological abnormalities.

Nutrition There was severe malnutrition in two cases before the onset of haemolytic anaemia.

Neutropenia In the miscellaneous group this was associated with ultimate severe liver dysfunction. Neutropenia was associated with possible liver dysfunction in one case of nocturnal haemoglobinuria. It occurred in the only case of acquired spherocytic jaundice, in which there were no biochemical tests of liver function.

Macrocytosis This was frequent, and was usually associated with normoblastic erythropoiesis. Reticulocytosis was not the main factor in the macrocytosis.

Reticulocytosis There was a difference in the usual reticulocyte level in cases with a similar haemoglobin level, suggesting that the marrow reaction was not solely in response to the degree of anaemia. Splenectomy in one case caused a sustained rise in reticulocytes with little effect on the level of

ASCITES IN CHRONIC DISEASE OF THE LIVER¹

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It has long been assumed that the main factor in the production of ascites in chronic liver disease is increased pressure in the portal circulation, the existence of which was deduced from the tendency to enlargement of collateral vessels and has now been proved by direct measurement of splenic vein pressures (Thompson, Caughey, Whipple, and Rousselot, 1937). There have always been difficulties, however, in accepting portal hypertension as the only cause of ascites in disease of the liver. In some cases, splenomegaly and oesophageal varices may be extreme, yet ascites may be absent, in others, ascites may appear so suddenly and develop so rapidly that it is hardly conceivable that increased pressure in the portal system could be the only factor responsible. Rolleston and McNee (1929) summarized the suggestions that had been made by various observers about other possible causes, and mentioned thrombosis of the radicles or trunk of the portal vein, 'toxaemia' causing increased permeability of capillaries, concomitant infection of the peritoneum, and associated cardiac failure. It can be definitely stated, however, that portal vein thrombosis, peritoneal infection, and cardiac failure are comparatively rare accompaniments of ascites in chronic liver disease. In our own series of 35 cases, portal vein thrombosis and superior mesenteric vein thrombosis were each found on one occasion only at autopsy, while peritoneal infection was not found. It is less easy to be dogmatic about damage to capillaries by toxaemia. The peripheral systemic vessels can certainly be damaged in disease of the liver, as is shown by the occurrence of spider naevi and palmar erythema (Bean, 1945), but it is not known whether the capillaries of the portal circulation are affected.

The fact that subacute and chronic liver disease is frequently associated with low plasma-albumin values, often accompanied by a rise in plasma-globulin, has been established by the work of many observers (Salvesen, 1929, Wiener and Wiener, 1930, Peters and Eisenman, 1933, Myers and Keefer, 1935, Snell, 1935, Foley, Keeton, Kendrick, and Darling, 1937, Kellermann, 1937, Tumen and Bockus, 1937, Post and Patek, 1942, Higgins, O'Brien, Stewart, and Wits, 1944, Turner, Snarely, Grossman, Buchanan, and Foster, 1944), and it has been suggested that the resulting diminution in plasma colloid osmotic pressure (C O P) is the other main

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and the fluid was invariably sterile on examination. In six cases the effusion appeared terminally and had not been noticed during life, but in one case it appeared nine months before death and was continuous, during this period 64 aspirations were made and approximately 230 pints of straw-coloured fluid of low protein content removed. All the patients with pleural effusions have died, but in one case the effusion first appeared with ascites five years before death and did not recur until the terminal phase of the illness. In six of the patients with pleural effusion oesophageal varices were identified.

The colloid osmotic pressure In our series of cases, 193 estimations of plasma-proteins are available, and provide a basis for an analysis of the part which may be played by variations in the plasma C O P in the production of ascites. The plasma-proteins were estimated by the micro-Kjeldahl technique with the use of sodium sulphate to precipitate the globulin (Howe, 1921). Unfortunately, there is no agreement among those who have studied the question as to the formula by which the plasma C O P may be calculated from the albumin and globulin levels. Govaerts (1925) thought that the plasma C O P could be estimated by using the formula

$$P = 7.54A + 1.95G,$$

P being the plasma C O P in cm of water, A the serum-albumin, and G the serum-globulin in grams per 100 c.c. Von Farkas (1926) proposed the formula $P = 6.8A + 2.5G$, amending this in a later paper (von Farkas, 1935) to $P = 7.9A + 1.3G$. Wells, Youmans, and Miller (1933), in a careful analysis of the C O P and protein fractions in 128 samples of serum, came to the conclusion that the formulae both of Govaerts (1925) and von Farkas (1926) were completely unreliable. They found that the osmotic pressure per gram of total protein ('specific osmotic pressure') bore a strictly linear relation to the albumin concentration, and that the total osmotic pressure could be accurately expressed by the formula $P = C(5.9A + 21.4)$, where P is the total osmotic pressure in mm of water, C the total protein, and A the albumin in grams per 100 c.c. The average difference between calculated and observed values for P in their series was only ± 11.5 mm of water. Wies and Peters (1937) made a similar study on 121 samples of serum from 103 subjects. Their measurements of osmotic pressure were systematically lower than those obtained by Wells, Youmans, and Miller (1933), presumably owing to differences in technique. They came to the conclusion that globulin exerts a small but definite osmotic action, and that a more accurate correlation between protein levels and C O P could be obtained by correcting the albumin and globulin figures from grams per 100 c.c. of serum to grams per 100 grams of water in serum, by means of the formula devised by Eisenman, Mackenzie, and Peters (1936). They proposed the formula

$$P = 60.9A_{100} + 22.9G_{100} - 50,$$

P being the osmotic pressure in mm of water, A_{100} and G_{100} the concentration of albumin and globulin in grams per 100 grams of water in serum. The average deviation between the values of P calculated from this formula and those measured directly was ± 27.6 mm, the error in measurement of C O P

factor in the production of ascites (Myers and Keefer, 1935, Kellermann, 1937, Post and Patek, 1942) There are technical difficulties in the accurate direct measurement of plasma C O P Most workers have therefore estimated the plasma-protein concentrations by biochemical methods, and from these values have calculated the C O P by means of empirical equations This procedure is not ideal, and indeed different authors have employed different formulæ. Nevertheless, the fact remains that the figures which the clinician will usually have at his disposal are the levels of plasma-albumin and plasma-globulin, and in the present paper the calculated osmotic pressure is used merely as the most convenient means of expression of the plasma-protein concentrations The conclusion from our own observations is that if the calculated osmotic pressure of the plasma-proteins in a case of ascites is normal, it is unlikely that the ascites is the result of chronic disease of the liver

The Present Investigation

The patients studied comprise 35 cases of subacute and chronic hepatitis (cirrhosis) whose aetiology and course are described in another paper (Kelsall, Stewart, and Witts, 1947) Ascites occurred in 19 of the 35 cases In 12 it was temporary or intermittent and in seven persistent The occurrence of ascites during the course of hepatitis should always be regarded as a serious event, but the outlook is by no means as gloomy as is commonly supposed Whilst six of the seven patients with continuous ascites died within five days to seven months from the onset of the effusion, one is still well enough to continue working after three years of continuous ascites and over 120 paracenteses In addition, six patients with temporary or intermittent ascites are still alive after one to four years, and five are at present free of ascites and leading normal lives The other six patients with temporary bouts of ascites died after periods which ranged from two months to five years after the first appearance of the ascites When ascites is temporary, the fluid is usually reabsorbed within a few weeks, but occasionally it may be present for as long as three to eight months before remission Temporary ascites may develop as a sequel to a severe haemorrhage, and it may disappear when the anaemia is repaired Ascites may also disappear spontaneously in the terminal phase of hepatitis, possibly as a result of dehydration Eleven patients with ascites came to autopsy, three were subjected to laparotomy, and one to laparoscopy In one of these 15 patients there was carcinomatosis, in another patient the peritoneum was described as opaque and thickened, and in the remainder the peritoneum was apparently normal This evidence of the infrequency of chronic peritonitis in cirrhosis confirms the larger experience of Nissen (1920)

Pleural effusions were found in 10 of the 13 patients who came to autopsy In two instances the effusion was confined to the right side of the chest and in the remainder it was bilateral In one case pleural effusion was associated with carcinomatosis In no instance was there any evidence of tuberculosis,

and the fluid was invariably sterile on examination. In six cases the effusion appeared terminally and had not been noticed during life, but in one case it appeared nine months before death and was continuous, during this period 64 aspirations were made and approximately 230 pints of straw-coloured fluid of low protein content removed. All the patients with pleural effusions have died, but in one case the effusion first appeared with ascites five years before death and did not recur until the terminal phase of the illness. In six of the patients with pleural effusion oesophageal varices were identified.

The colloid osmotic pressure In our series of cases, 193 estimations of plasma-proteins are available, and provide a basis for an analysis of the part which may be played by variations in the plasma C O P in the production of ascites. The plasma-proteins were estimated by the micro-Kjeldahl technique with the use of sodium sulphate to precipitate the globulin (Howe, 1921). Unfortunately, there is no agreement among those who have studied the question as to the formula by which the plasma C O P may be calculated from the albumin and globulin levels. Govaerts (1925) thought that the plasma C O P could be estimated by using the formula

$$P = 7.54A + 1.95G,$$

P being the plasma C O P in cm of water, A the serum-albumin, and G the serum-globulin in grams per 100 c.c. Von Farkas (1926) proposed the formula $P = 6.8A + 2.5G$, amending this in a later paper (von Farkas, 1935) to $P = 7.9A + 1.3G$. Wells, Youmans, and Miller (1933), in a careful analysis of the C O P and protein fractions in 128 samples of serum, came to the conclusion that the formulae both of Govaerts (1925) and von Farkas (1926) were completely unreliable. They found that the osmotic pressure per gram of total protein ('specific osmotic pressure') bore a strictly linear relation to the albumin concentration, and that the total osmotic pressure could be accurately expressed by the formula $P = C(5.9A + 21.4)$, where P is the total osmotic pressure in mm of water, C the total protein, and A the albumin in grams per 100 c.c. The average difference between calculated and observed values for P in their series was only ± 11.5 mm of water. Wies and Peters (1937) made a similar study on 121 samples of serum from 103 subjects. Their measurements of osmotic pressure were systematically lower than those obtained by Wells, Youmans, and Miller (1933), presumably owing to differences in technique. They came to the conclusion that globulin exerts a small but definite osmotic action, and that a more accurate correlation between protein levels and C O P could be obtained by correcting the albumin and globulin figures from grams per 100 c.c. of serum to grams per 100 grams of water in serum, by means of the formula devised by Eisenman, Mackenzie, and Peters (1936). They proposed the formula

$$P = 60.9A_{w} + 22.9G_{w} - 50,$$

P being the osmotic pressure in mm of water, A_w and G_w the concentration of albumin and globulin in grams per 100 grams of water in serum. The average deviation between the values of P calculated from this formula and those measured directly was ± 27.6 mm, the error in measurement of C O P

TABLE I
GROUP A

Sex	Splenic enlarge- ment	Oesophageal varices	Date	Total plasma- protein (gm per 100 cc)	Plasma albumin (gm per 100 cc)	Plasma globulin (gm per 100 cc)	C O P (Wells, You- mans, and Miller) (mm of water)	C O P (Wies and Peters) (mm of water)	Clinical ascites	Clinical pleural effusion
M	—	—	20 5 42	4 7	2 4	2 0	167	152	—	—
F	—	—	0 8 43	6 7	1 02	5 0	207	177	+	—
			11 8 43	6 85	1 57	5 1	210	177	+	—
			0 0 43	7 05	1 0	5 6	240	212	+	—
F	—	—	19 1 43	9 0	4 0	?	405	?	—	—
			6 3 43	8 55	2 75	5 5	321	268	—	—
			10 4 43	8 0	2 48	6 1	322	266	—	—
			7 5 43	8 0	2 5	5 80	311	261	—	—
			12 6 43	8 0	2 04	5 7	267	225	—	—
			2 0 43	9 0	1 2	7 7	256	221	+	—
F	—	—	31 7 44	8 5	2 5	6 0	307	264	—	—
			8 8 14	8 8	2 5	6 03	318	265	—	—
			24 8 44	8 35	2 5	5 0	302	253	—	—
			3 11 44	8 75	2 8	?	332	?	—	—
			9 3 45	9 55	2 2	7 12	326	274	—	—
			1 0 45	8 45	2 55	5 6	313	264	—	—
			21 9 45	8 55	3 5	4 8	359	300	—	—
			14 12 45	7 97	3 06	3 95	343	288	—	—
M	—	—	16 11 43	7 05	3 1	4 0	304	252	—	—
			20 6 44	6 92	3 20	3 15	281	239	—	—
			5 1 45	8 65	3 0	4 45	369	298	—	—
			24 8 45	7 2	2 55	4 2	262	219	—	—
			20 11 45	9 2	3 88	4 64	407	323	—	—
			5 4 40	10 2	3 96	5 54	457	354	—	—
M	—	—	9 1 44	7 1	3 75	3 0	309	269	—	—
			14 1 44	6 6	3 4	3 0	274	244	—	—
			20 1 44	6 8	3 45	3 1	284	256	—	—
			26 1 44	6 75	3 45	3 0	282	248	—	—
			2 2 44	7 0	3 5	3 2	294	257	—	—
			9 2 44	7 3	3 7	3 2	316	270	—	—
			16 2 44	7 2	3 7	3 1	311	268	—	—
			23 2 44	7 5	3 95	3 2	335	287	—	—
			11 3 44	7 7	4 3	3 1	360	308	—	—
M	—	—	12 3 41	8 0	4 42	3 25	380	321	—	—
			9 5 41	7 8	4 5	3 0	374	319	—	—
F	—	—	3 11 44	8 2	5 6	2 3	446	375	—	—
			14 12 44	6 8	4 5	1 95	320	291	—	—
			21 12 44	6 75	4 42	2 18	320	291	—	—
			16 3 45	7 0	4 8	?	348	?	—	—
			29 4 46	7 4	4 6	2 5	359	312	—	—
F	—	—	21 1 44	7 6	4 4	2 7	360	305	—	—
			17 4 44	7 85	4 93	2 57	396	337	—	—
F	—	—	9 8 45	6 55	1 7	4 55	206	172	—	—
			22 8 45	7 0	1 9	4 8	228	192	—	—
			11 9 45	6 42	1 82	4 35	206	174	—	—

TABLE II
GROUP B

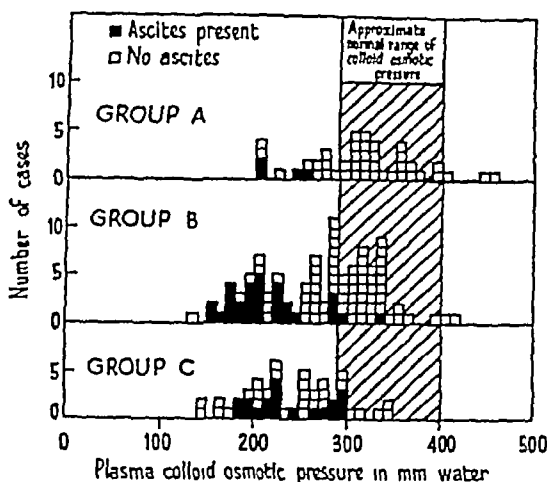
F Sex	Splenic enlarge- ment	Oesophageal varices	Date	Total plasma- protein (gm per 100 cc)	Plasma albumin (gm per 100 cc)	Plasma globulin (gm per 100 cc)	C O P (Wells, You- mans, and Miller) (mm of water)	C O P (Wicks and Peters) (mm of water)	Clinical ascites	Clinical pleural effusion
	—	+	23 5 42	5 0	3 6	?	213	?	+	—
			28 5 42	5 0	3 0	1 7	195	184	+	—
M	—	+	11 3 43	7 1	1 98	4 9	235	199	+	—
			23 7 43	8 3	3 2	4 9	334	282	—	—
			31 12 43	8 4	2 2	6 0	289	244	+	—
			10 1 44	7 15	1 9	5 05	233	198	+	—
			19 1 44	7 15	2 0	5 0	237	203	+	—
			26 1 44	7 4	1 8	5 4	237	201	+	—
			14 2 44	7 1	1 9	5 0	231	197	+	—
			7 3 44	6 8	1 5	5 1	206	172	+	+
M	—	+	18 2 42	5 63	2 49	2 57	203	173	+	—
			26 10 42	5 5	3 14	2 2	219	206	—	—
F	+	—	29 5 42	5 5	2 24	2 9	190	165	—	+ (post pneumonic)
			16 4 43	5 9	2 42	3 16	210	183	—	—
			21 7 43	6 1	2 58	3 2	223	195	—	+ } (carci-
			21 8 43	5 8	2 3	?	203	?	—	+ } noma)
F	+	—	4 6 46	7 4	3 8	3 1	324	275	—	—
F	—	+	24 2 44	6 95	2 7	4 0	259	224	—	—
			26 5 44	5 85	2 24	3 53	202	181	+	—
			8 7 44	5 14	1 54	3 27	157	128	+	—
			21 7 44	5 4	1 8	3 2	173	143	+	—
			18 9 44	4 95	1 8	?	158	?	+	—
F	—	+	1 12 41	8 0	2 5	5 2	289	243	—	—
			1 1 42	8 2	2 56	5 5	299	254	—	—
			6 3 42	9 0	2 8	5 9	341	282	—	—
			16 4 42	9 2	2 2	6 7	316	263	—	—
			26 9 42	9 0	1 6	7 2	278	235	—	—
M	+	—	18 2 42	8 1	4 75	3 1	400	339	—	—
			6 8 42	8 7	3 0	5 5	340	285	—	—
			14 8 43	8 1	2 8	5 1	307	260	—	—
			25 2 44	8 5	2 8	5 4	322	269	—	—
			1 9 44	9 1	3 1	5 5	361	292	—	—
			23 3 45	8 24	3 2	4 7	332	277	—	—
			26 3 46	9 6	3 6	5 6	409	329	—	—
F	+	—	1 4 43	9 15	4 25	4 5	425	344	—	—
			Feb 44	6 7	4 7	1 7	329	297	—	—
			16 4 45	7 2	4 38	2 5	340	297	—	—
F	+	—	9 2 45	7 75	2 8	4 05	294	248	—	—
			17 5 45	7 98	3 05	4 4	314	259	—	—
			8 4 46	8 6	2 6	5 6	316	261	—	—
F	+	—	10 6 41	6 6	3 0	3 3	258	226	—	—
			18 2 42	7 6	3 7	3 6	328	281	—	—
			27 1 43	7 09	3 86	2 8	313	271	—	—
			7 7 43	7 6	3 74	3 4	330	279	—	—
			19 4 44	6 82	3 52	2 94	288	251	—	—
			11 4 45	6 6	3 5	2 8	277	246	—	—
			4 7 45	6 7	3 69	2 71	289	256	—	—
			15 4 46	7 3	3 7	3 97	315	272	—	—

Sex	Splenic enlargement	Oesophageal varices	Date	Total plasma-protein (gm per 100 cc)	Plasma-albumin (gm per 100 cc)	Plasma globulin (gm per 100 cc)	C O P (Wells, Youmans, and Miller) (mm of water)	C O P (Wies and Peters) (mm of water)	Clinical ascites	Clinical pleural effusion
M	+	-	20 0 41	6 0	4 0	2 34	207	267	+	-
			18 11 43	6 86	3 65	2 9	204	259	-	-
			16 6 44	5 57	3 35	2 02	229	215	+	-
			25 9 44	6 55	3 8	2 55	287	259	+	-
			16 2 45	6 41	4 1	2 0	202	265	+	-
F	+	-	23 7 43	6 55	2 46	3 92	235	206	-	-
			31 7 43	6 2	2 5	3 7	224	202	-	-
			16 9 43	5 65	2 75	2 6	213	191	+	-
			7 12 43	4 55	1 75	2 56	144	124	+	-
			4 1 44	5 95	2 25	3 4	206	168	+	-
			11 1 44	5 3	2 0	3 1	176	154	+	-
			19 1 44	5 7	1 8	3 7	183	156	+	-
			8 3 44	5 4	2 0	3 1	170	154	+	-
			6 10 44	5 47	2 5	2 62	198	175	+	-
			1 12 44	5 7	2 2	3 1	190	167	+	-
			16 2 45	5 32	2 27	2 7	185	161	+	-
			8 4 46	6 2	3 3	2 5	253	225	+	-
M	+	-	27 1 43	6 0	1 8	3 9	192	161	+	-
			16 2 43	6 4	2 04	4 1	214	182	+	-
			21 7 43	7 15	3 16	3 73	286	248	-	-
M	+	-	14 4 44	6 44	3 44	2 73	208	240	-	-
			17 5 44	7 1	2 82	3 44	270	268	-	-
			7 6 44	7 0	3 76	2 77	305	263	-	-
			20 6 44	6 58	3 43	2 74	274	239	-	-
			27 10 44	7 7	4 1	3 1	351	295	-	-
			24 11 44	7 2	3 7	3 0	311	265	-	-
			3 8 45	7 0	3 0	3 0	274	234	-	-
			30 8 45	5 9	2 5	3 4	213	194	-	-
			18 9 45	7 0	2 8	3 8	265	226	-	-
			12 10 45	7 52	3 56	3 5	319	269	-	-
			9 1 46	7 9	3 2	4 15	318	263	-	-
M	+	-	21 6 45	6 77	2 8	3 77	257	224	-	-
			29 6 45	6 8	3 1	3 4	270	235	-	-
			18 3 46	7 25	2 7	4 35	271	233	-	-
			25 3 46	7 1	2 8	4 0	269	231	-	-
M	+	-	1 3 43	8 0	3 5	4 1	336	281	-	-
			9 3 43	7 4	3 3	3 9	302	262	-	-
			19 3 43	7 15	3 2	3 75	288	251	-	-
			29 3 43	7 3	3 3	4 0	298	264	-	-
			29 4 43	8 05	4 2	3 55	372	314	-	-
			10 6 43	7 3	4 0	3 17	328	289	-	-
			11 9 43	7 35	4 3	2 8	344	300	-	-
			21 1 44	6 7	4 2	2 2	309	277	-	-
			8 9 44	7 2	4 5	?	345	?	-	-
			14 4 45	7 4	4 57	2 5	358	310	-	-
M	+	-	30 1 43	9 0	2 8	5 85	341	281	+	-
			15 10 43	6 85	3 65	2 9	294	259	-	-
			16 2 45	6 85	4 72	1 8	337	301	-	-
			25 5 45	6 92	4 13	2 64	317	284	-	-
			9 11 45	6 33	4 6	1 59	307	287	-	-
			26 4 46	7 35	4 3	2 7	344	198	-	-

TABLE III
GROUP C

Splenic enlarge- ment	Oesophageal varicæ	Date	Total plasma- protein (gm per 100 cc)	Plasma-albumin (gm per 100 cc)	Plasma globulin (gm per 100 cc)	C O P (Wells, You- mans, and Miller) (mm of water)	C O P (Wies and Peters) (mm of water)	Clinical ascites	Clinical pleural effusion
+	+	29 10 43	65	17	485	204	179	+	—
		2 11 43	635	14	48	188	158	+	—
		8 11 43	635	14	48	188	158	+	—
		17 11 43	76	15	60	230	196	+	—
+	+	5 2 42	85	246	57	305	254	+	—
		25 4 42	604	12	47	172	142	+	—
		23 5 42	59	14	?	175	?	+	—
+	+	15 10 42	77	40	33	346	293	—	—
		30 1 43	72	288	389	276	234	—	—
		29 6 43	63	33	242	257	223	—	—
		10 9 43	60	30	27	235	209	—	—
		17 9 43	68	30	34	266	229	—	—
		28 9 43	77	30	44	301	255	—	—
		3 4 44	406	255	221	181	167	—	—
		26 4 44	61	262	32	225	198	—	—
		3 10 44	685	20	44	227	188	+	—
+	+	1 3 45	705	38	289	309	269	—	—
		28 3 45	695	362	296	297	259	—	—
		27 7 45	735	375	32	320	274	—	—
		Dec 45	60	30	30	235	217	+	—
		1 5 46	70	31	32	278	231	—	—
+	+	3 6 43	753	238	478	267	223	+	—
		17 6 43	77	261	469	283	237	—	—
		10 9 43	89	205	57	345	287	—	—
		28 1 44	865	32	49	348	283	—	—
		20 9 44	787	27	48	294	246	+	—
		22 1 45	685	21	44	231	194	+	—
		12 2 45	71	238	441	252	213	+	—
		20 2 45	763	251	474	276	231	+	—
		26 2 45	81	266	505	300	249	+	—
		14 6 45	615	108	369	203	168	+	—
		7 9 45	85	23	63	297	258	+	—
		31 1 46	655	208	447	220	194	—	—
+	+	6 11 44	59	22	35	203	177	—	—
		18 12 44	60	224	353	208	181	—	—
		20 12 44	66	238	40	234	202	—	—
		5 2 45	705	255	400	257	216	—	—
		4 4 45	688	285	382	263	229	—	—
		3 10 45	557	270	28	208	192	—	—
		16 1 46	67	304	366	263	237	—	—
+	+	10 8 44	715	25	42	258	216	—	—
		17 8 44	80	20	56	260	219	—	—
		22 9 44	77	28	?	202	?	+	—
		8 10 44	62	21	38	209	179	+	—
		23 3 45	645	199	423	214	182	—	+
		12 4 45	695	218	42	238	195	—	+
		21 6 45	51	15	?	154	?	+	—
		15 10 45	51	149	724	154	124	+	—
		14 12 45	692	188	474	225	189	+	—

in duplicate samples of serum being approximately 10 mm. These inconsistencies presumably arise from the technical difficulties involved in accurate measurement of plasma osmotic pressures. Von Farkas (1935) pointed out the great variations in normal plasma C O P obtained by different investigators, even when using the same technical method. The disadvantages of using a formula are especially great in chronic disease of the liver, where



the plasma-proteins may be altered qualitatively as well as quantitatively. In the present paper the formula of Wells, Youmans, and Miller (1933) has been used in calculating the plasma C O P, since it seems to show the best fit with directly determined values. In the tables we have also given the figures obtained with the formula of Wies and Peters (1937). The C O P by their formula is always some 10 to 20 per cent lower than by Wells, Youmans, and Miller's formula, the difference tending to be both absolutely and relatively greater at high levels of C O P.

In order to differentiate between cases with varying degrees of portal hypertension, the patients have been placed in three groups, which it is thought may fairly be taken to represent, in a rough way, those with absent or slight, moderate, and severe portal hypertension.

Group A Splenic enlargement not detected clinically. Oesophageal varices not demonstrated.

Group B Splenic enlargement detected clinically or oesophageal varices demonstrated radiographically, by oesophagoscopy, or at autopsy.

Group C Splenic enlargement detected clinically and oesophageal varices demonstrated.

Group A (absent or slight portal hypertension) contains 10 patients, from whom 45 estimations of plasma-proteins, made at times when the presence or absence of ascites was recorded, are available (Table I). Group B (moderate portal hypertension) contains 18 patients (13 with splenomegaly but no

varices, five with varices but no splenomegaly), from whom 99 such estimations are available (Table II) Group C (severe portal hypertension) contains seven patients, from whom 49 such estimations are available (Table III) Although we have attempted to grade the portal hypertension in accordance with the physical signs, it should be noted that these signs are themselves evidence that a compensatory mechanism for relieving the undue pressure has been established, and may actually indicate some relief of a pre-existing increased pressure Thus while a patient with an enlarged spleen and oesophageal varices must at some time have had a high level of portal pressure, this may have been partially relieved by the development of a satisfactory collateral circulation

The plasma C O P s, calculated according to the formula of Wells, Youmans, and Miller (1933) to the nearest 10 mm of water, have been plotted graphically (p 270) to show the relationship to the presence or absence of ascites It will be seen that the proportion of plasma C O P levels below the generally accepted normal range of 300 to 400 mm of water rises from approximately 33 per cent in Group A to 58 per cent in Group B and 79 per cent in Group C, this represents the greater chronicity and severity of the disease in cases showing evidence of increasing portal pressure Ascites was present on four occasions at the time of protein estimations in patients from Group A, in spite of the absence of other evidence of portal hypertension, and the plasma C O P was well below normal values on each occasion In Group B all plasma C O P values except two were below normal when ascites was present, and in Group C all except three Nevertheless, it is obvious that there is no level of plasma C O P which can be precisely correlated with the presence or absence of ascites Values as low as 200 mm of water may occasionally occur without clinical evidence of ascites, even in the presence of severe portal hypertension The general tendency, however, for ascites to be present when plasma C O P is low and absent when it is normal or high is clearly shown All the patients with pleural effusion showed a low level of colloid osmotic pressure

Discussion

Peters and Eisenman (1933), in a small group of patients with cirrhosis or toxic hepatitis, found no clear correlation between ascites and albumin levels, but Post and Patek (1942), in a study of 61 cases of cirrhosis, reported that the serum-albumin was significantly lower in patients with ascites than in those without, though there was considerable overlap between the two groups Kellermann (1937), using direct measurement of plasma C O P, found that cases of cirrhosis tended to have low C O P values, those with ascites having lower pressures than those without Butt, Snell, and Keys (1939), also using direct measurement, found that plasma C O P was below normal in all cases of ascites in a group of 23 patients with cirrhosis Ralli, Robson, Clarke, and Hongland (1945), on the other hand, in a study of

14 patients with alcoholic cirrhosis, reported that the levels of plasma-albumin and C O P (estimated by the formula of Wies and Peters, 1937) were of the same order in patients with and without ascites, though they were below normal levels in both groups, moreover, when ascites disappeared during treatment, it did so before there was any significant change in the level of plasma-albumin. Pursuing another line of inquiry, they observed that the urine of the patients with ascites had a greater anti-diuretic effect when injected into hydrated rats than had urine from the patients without ascites or from normal subjects. They therefore made the tentative suggestion that a further factor in the production of ascites in patients with cirrhosis may be failure of the liver to destroy some anti-diuretic principle. Our own results show that ascites occurs but rarely in subacute and chronic hepatitis unless the plasma colloid osmotic pressure is below normal levels. Low colloid osmotic pressures, however, do not necessarily lead to the development of an abdominal effusion, moreover, although in the individual patient the plasma C O P was usually lower when ascites was present than when it was absent, this was not invariable, irrespective of the formula used for estimation. It is possible that some of these discrepancies are due to the acknowledged difficulty of detecting small abdominal effusions with certainty, and to occasional inadequacy of the clinical records due to shortage of experienced medical staff during the war years.

During the last 50 years the study of oedema and of the accumulation of fluid in the tissues has been dominated by Starling's concept of a balance between the filtration pressure of the blood in the capillaries and the colloid osmotic pressure of the plasma. Nevertheless, in hepatic disease, as in Bright's disease, there is much to suggest that additional factors must be concerned, and we do not pretend that a rise in portal venous pressure and a fall in the colloid osmotic pressure of the plasma are the sole causes of ascites in disease of the liver. Not only may the walls of the capillary, the filtration membrane, be changed in permeability, but it is also possible that the channels for the reabsorption of fluid from the peritoneal cavity may be obstructed by chronic peritonitis. Moreover, when the metabolic functions of the liver are disturbed, there may be an interference with the excretion of fluid by the kidney, as Ralli, Robson, Clarke, and Hoagland (1945) suggested. We can also imagine that the portal venous pressure, like the systemic blood-pressure, undergoes variations, and it is therefore not surprising that neither in the individual patient nor in the group as a whole is there perfect correlation between the calculated osmotic pressure of proteins and the appearance or disappearance of ascites. An exact study of the mechanism of ascites would demand the direct measurement of the colloid osmotic pressure of the proteins and the blood-pressure in the portal vein, and neither of these estimations is feasible in routine clinical work. Nevertheless, the correlation between ascites in hepatic disease and the colloid osmotic pressure of the plasma, as calculated from the protein values, is a high one and can be of much significance in the diagnosis of ascites. Our

own data and those recorded in the literature show that it is unusual for ascites to develop in hepatitis unless the colloid osmotic pressure is below 300 mm or the serum-albumin below 2.5 gm per 100 cc. This is a useful differentiation from the ascites of heart-disease, malignant disease, and peritonitis, where plasma-protein levels are not so remarkably depressed. The absence of ascites in the early stages of splenic anaemia, when the portal pressure may be as high or higher than in a case of alcoholic cirrhosis, is explained by the fact that the metabolic functions of the liver and therefore the level of serum-proteins are well maintained.

Summary

1 Temporary or persistent ascites was observed in 19 out of a series of 35 cases of subacute and chronic hepatitis.

2 The presence or absence of ascites was compared with the colloid osmotic pressure of the plasma, as calculated from 193 estimations of plasma-proteins. Ascites was rarely found when the colloid osmotic pressure of the plasma was within normal limits.

3 Although the correlation between ascites and low colloid osmotic pressure of the plasma-proteins in hepatic disease is by no means absolute, the dependence of the ascites on a low level of plasma-proteins is a useful point in diagnosis.

4 Pleural effusion, which is not uncommon in the later stages of hepatitis, likewise appears to be related to the fall in the concentration of plasma-proteins.

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STUDIES ON THE MECHANISM OF THE FANCONI SYNDROME¹

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With Plates 11 and 12

IN 1926 Schier and Stern described a peculiar syndrome in children characterized by rickets resistant to vitamin D, low serum inorganic phosphorus, and renal glycosuria. Similar cases were reported by Boyd in 1927 and 1928, Fanconi in 1931, and de Toni in 1933. In the following year Debré, Marie, Cléret, and Messimy, in describing another case, made the additional observation that there was an excessive urinary excretion of organic acids bound to mineral cations. The ammonia coefficient of the urine was also abnormally high. Van Creveld (1934) contributed a case in which the liver was enlarged and unevenly fibrotic, and Hunter in 1935 first recognized the syndrome in an adult and will shortly be reporting a series of such cases. Fanconi published two more cases in 1936 and was the first to suspect that the large amounts of organic acids in the urine might be due, at least in part, to amino-aciduria. This was confirmed in another case by McCune, Mason, and Clarke (1943), who have written an excellent review of the subject. In many of the reported cases of the syndrome there have been abnormal deposits of cystine in the tissues, with associated cystinuria in some (Lignac, 1924, 1938, Russell and Barrie, 1936). The following case, which was originally diagnosed by Dr Donald Hunter, is presented not primarily because of its rarity or intrinsic clinical interest, but because the investigations performed on the patient shed light not only on the nature of the syndrome itself, but also on the mechanism of several related conditions.

Case Report

The patient was a surveyor by profession and 34 years of age when the present study began in April, 1945. He then complained of persistent pains in the back for four years and of radiation of the pains into both thighs for about three years. Soon after the onset of symptoms he noticed gradually increasing difficulty in walking, especially for the first few steps. At about this time (1942) he was admitted to a provincial hospital where a diagnosis of diabetes mellitus was made. Treatment was started with 10 units of soluble insulin twice a day and the patient responded by having attacks of fainting and blurred vision relieved by taking sugar. On his return to

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London he was admitted to a teaching hospital where he was shown to have diabetes mellitus with a low renal threshold, and many investigations, including a skin biopsy, were made. Presumably the diagnosis of haemochromatosis was entertained at that time. On discharge he was taking insulin at the rate of 24 units daily, and his symptoms still persisted with varying severity. Later in 1942 he started to avoid lifting weights, although he had not noticed any impairment of his muscular strength. Early in 1943 he first experienced 'collapsing incidents' in which his legs seemed to give way under him, and this was the immediate reason for his attending the out-patient diabetic clinic at University College Hospital. Here his glycosuria was shown to be due to mild diabetes with a low renal threshold. He was found to have albuminuria and his blood-urea was 30 mg per 100 c.c. His special diet and insulin were discontinued, but the collapsing attacks were unaffected. He attended the National Hospital, Queen Square, but no neurological abnormalities were found, and he was referred back to University College Hospital, where he was admitted in April, 1945. By that time he had multiple pains accentuated by movement, and could walk only a few waddling steps. He said that in the previous three years he had lost $3\frac{1}{2}$ stone in weight, although his appetite had remained good, and that he suspected that he was getting shorter. His diet had been adequate, especially in meat, of which he was particularly fond. As a boy he had had severe knock-knee deformity for which bilateral osteotomy was performed, but otherwise he had had only the common childhood infections. The family history was of interest in that his mother and her four sisters, but not her brother, all had either gross deformities, glycosuria, or hepatomegaly, or a combination of these. There was no history of consanguinity in his parents or in his mother's parents.

Physical examination. On examination the patient was a small, rather pale man, with a square head, short, protruberant abdomen, and widened femoral condyles. Findings of interest were a liver palpable two inches below the right costal margin in the nipple line and a mass thought to be the spleen, with its tip palpable half an inch below the left costal margin. The liver was firm, but not tender, and had an irregular surface and edge. No abnormalities were found in the cardiovascular, respiratory, or nervous systems. When the patient was asked to grip hard with his hands he complained of a subsequent aching in the forearm. The blood-pressure was 108/80, and the temperature, pulse, and respiration normal. The urine was almost constantly alkaline and contained slight to moderate amounts of albumen. There was a constant glycosuria which was shown to be partly renal in type. The sediment was normal. A full blood-count and platelet-count were normal. A sternal marrow puncture disclosed some abnormally large megakaryocytes. The blood Wassermann reaction was negative and the basal metabolic rate was +20 per cent and +17 per cent on successive days some eight months before death.

Radiology. X-rays showed marked generalized osteomalacia and numerous roughly symmetrical pseudofractures of the type described by Looser (1920) and Milkman (1934). The dorsolumbar spine was scoliotic with a 'fish disk' appearance of the lumbar vertebrae. There were many pseudofractures of the ribs with no callus formation. There was a triradiate deformity of the pelvis which displayed several pseudofractures, especially in the pubic rami. In the arms also there were several pseudofractures, including strikingly symmetrical ones in the neck of each radius. There was evidence of old rickets in the lower ends of the femora and in the upper ends of the tibiae. A genu

valgum deformity persisted in spite of old bilateral osteotomies. The sella turcica was normal. The lamina dura in the teeth sockets were normally outlined and there was an apical abscess under a molar tooth. An intravenous pyelogram failed to outline the calyces and renal pelves. A calcified mesenteric gland was seen, but there was no evidence of either nephrolithiasis or nephrocalcinosis.

Chemical pathology (Table I) The serum-calcium and alkaline phosphatase were normal, but the serum inorganic phosphorus was conspicuously low. The liver function was not grossly abnormal, the Takata-Ara, cephalin cholesterol flocculation, and colloidal gold tests being negative, and the prothrombin index normal. The plasma-proteins were not very abnormal, but the proportion of albumen decreased during the course of the disease. The serum-bilirubin was slightly raised. The kidney function was moderately impaired as shown by intravenous pyelography and urea clearance. The blood-urea was normal.

Mineral metabolism (Table II) The ionic equation of the plasma showed that there was an excess of cations amounting to 20 m eq, not more than 12 of which could be attributed to combined analytical error. It was concluded that unidentified acids must have neutralized the excess cation. In spite of the presence of these acids in the plasma, the urine was almost constantly alkaline, largely as a result of increased ammonia production. The ammonia coefficient was two to five times normal (amino-nitrogen not included in total nitrogen).

Amino-acid and sulphur metabolism A special study of these features has been made by one of us (Dent, 1947). The findings can be summarized as follows. The daily output of amino-nitrogen in the urine averaged about 1,000 mg (normal 100 to 400 mg), and this amount represented some 10 per cent of the total urinary nitrogen (normal 1 to 3 per cent). The following amino-acids were identified in the urine in abnormally large amounts, aspartic acid, glutamic acid, glycine, serine, alanine, threonine, valine, leucine (and/or isoleucine), tyrosine, arginine, hydroxyproline, and phenylalanine. Citrulline, histidine, and amino-butyric acid were present in smaller amounts, but certainly in excess of normal. Whereas cystine and methionine were present in normal quantities, there was a disproportionately large amount of hydroxy-amino-acids. In addition a peptide containing serine and glycine was almost constantly present. Despite the excess excretion, the blood amino-nitrogen was normal at 6.3 mg per 100 cc (23.1.1946). Concurrent estimations of the total 24-hour output of glucose and amino-nitrogen in the urine showed that, although there were wide day-to-day variations, there was a straight-line relationship between them. This can be expressed by the formula

$$\text{Amino-nitrogen (gm)} = 0.064 \times \text{glucose (gm)} + 0.280$$

The urinary sulphur partition was within normal limits, the average findings being sulphate sulphur 80 per cent, ethereal sulphur 9 per cent, and neutral sulphate 11 per cent. A methionine tolerance test (Albanese, Frankston, and Irby, 1944), in which the urinary methionine was estimated after an oral dose of 1.5 gm, was normal, and there was no evidence of abnormal metabolism when cystine and methionine were given in 8 and 10 gm amounts respectively by mouth.

Course and treatment While in the ward the patient had various pains in the chest, back, and legs, made worse by movement. Treatment with calcium salts and vitamin D was started on 6.6.1945. He was given calcium gluconate gr 90 per diem and calciferol at the rate of 150,000 units, and later

300,000 units, per diem. On this treatment the serum inorganic phosphorus rose from 2.4 to 3.9 mg per 100 c.c., the alkaline phosphatase from 5 to 62.8 units (King and Armstrong, 1934), and the serum-calcium was not

TABLE I

*Routine Investigations**Renal function tests*

Urinary sediment normal Slight to moderate albuminuria

Concentration and dilution test, range of specific gravity 1,022 to 1,004

Blood urea 21.7 1945 48 mg per 100 c.c.

19.1 1946 39 mg per 100 c.c.

Standard urea clearance 21.7 1945 26 per cent of average normal (This may have been affected by the alkaline therapy)

Intravenous pyelography, renal pelvis, and calyces not outlined

Glucose tolerance tests

	22.2 1944	Jan 1945*	5.2 1945*	29.4 1945
Fasting level	117	90	75	125
$\frac{1}{2}$ hour	119	—	—	—
$\frac{1}{4}$ "	217	155	125	—
$\frac{3}{4}$ "	226	—	—	—
1 "	202	225	100	210
1 $\frac{1}{2}$ hours	186	205	140	—
2 "	174	175	133	130
2 $\frac{1}{2}$ "	145	—	—	—
3 "	106	—	—	105
Urine	Trace of sugar in fasting specimen + at 1 hour	Sugar in all specimens	Sugar in all specimens	Trace of sugar at 0 and $\frac{1}{2}$ hour, + at 1 and 1 $\frac{1}{2}$ hours, trace at 2 hours

The urinary sugar was identified as glucose by the osazone and fermentation tests

* Test done at National Hospital, Queen Square

Liver function tests

5.5 1945 Takata Ara, cephalin cholesterol flocculation, and colloidal gold tests, all negative. Serum-bilirubin 0.6 mg per 100 c.c. Blood cholesterol 195 mg per 100 c.c.

Calcium and phosphorus metabolism and plasma protein estimations

Date	Serum-calcium (mg per 100 c.c.)	Plasma-phosphorus (mg per 100 c.c.)	Alkaline phosphatase (units)	Plasma proteins		
				Total albumen (gm per 100 c.c.)	Albumen globulin ratio	
5.5 1945	—	—	5	6.4 4.9	3.2	1
2.6 "	10.4	2.4	—	—	—	—
23.7 "	10.4	3.9	—	—	—	—
7.8 "	10.5	3.2	62.8	6.9 4.92	2.5	1
Treatment discontinued						
18.9 1945	11.3	1.8	—	—	—	—
28.1 1946	—	—	—	5.7 3.74	1.9	1

altered. There was concomitant healing of the pseudofractures and marked improvement in the patient's symptoms. The osteomalacia also decreased, as judged by comparison of serial skiagrams with those of a control. When, on 7.8 1945, the patient left the hospital after a stay of 14 weeks he was free of pain and could walk almost normally except that his gait was still rather wide-based. He discontinued treatment on going home, and three

months later the serum inorganic phosphorus had fallen to 1.58 mg per 100 c.c. and symptoms were just starting to return. He first complained of aching lower abdominal pain. Then his abdomen gradually enlarged. The

TABLE II
Special Investigations

Ionic equilibrium

BLOOD (7.8.1945)

	Mg per 100 c.c.	Meq per litre		Mg per 100 c.c.	Meq per litre
Plasma chloride	379	107	Sodium	360	155
Plasma bicarbonate	—	24.8	Potassium	16.5	4.2
Plasma inorganic phosphorus	3.2	1.6	Calcium	10.5	5.2
Plasma-protein	6.910	12	Magnesium	1.68	1.3
Total acid		145.4	Total base		165.7

Of the excess (20 m.eq.) of base, 12 m.eq. may be accounted for by the combined analytical error. The remainder is presumably accounted for by unidentified acids.

URINE (7.8.1945)

	Mg per 100 c.c.	Meq per litre		Mg per 100 c.c.	Meq per litre
Chloride	266	81	Sodium	156	64
Bicarbonate	—	—	Potassium	131	33.6
Phosphate	35.6	18.2	Calcium	20.4	10.2
Protein	0	0	Magnesium	5	4
Sulphate	23.6	14.8	Ammonium	54.4	32
		114			143.8

Reaction of body fluids

		Before breakfast	After breakfast
28.4.1945	Urinary pH	6.68	5.98
	Blood pH	—	7.58
16.7.1945	Urinary pH	8.4	7.8
	Ammonia coefficient	32%	23%
27.7.1945	Random sample of urine pH	7.4	—
	Ammonia coefficient	21.5%	—
7.8.1945	24 hour specimen of urine	—	—
	Ammonia coefficient	9.6%	—

appetite fell off and flatulence became a prominent symptom. By the beginning of January, 1946, four months after leaving hospital, signs of ascites were discovered and about this time he passed melaena stools. On re-admission to the ward there was slight oedema of the ankles and legs, and ascites which made it difficult to palpate the liver. The presence of blood in the intestine was confirmed by repeated examination of the stools, and there was an evident anaemia. Three pints of whole blood were transfused and the haemoglobin was then 72 per cent (Haldane). There was symptomatic improvement as well as disappearance of the oedema, but the patient started a series of haematemeses. He had several more transfusions, but his condition rapidly deteriorated during the second and third weeks of his stay in hospital. There was loss of appetite, loss of flesh, and progressively increasing ascites, while the attacks of lower abdominal colic continued, lasting half to one hour at a time. Two days before he died he became very weak, dehydrated, and irrational. He then lapsed into coma with deep sighing respirations of 24 per minute, a pulse-rate of 120, and temperature of 98 to 99.5° F.

Post-mortem examination (performed by Professor G R Cameron, nine hours after death) The body was that of a short sallow man showing considerable wasting, especially in the upper limbs. There was no icterus. The chest was barrel-shaped, but showed none of the deformities characteristic of rickets. There was slight oedema of the ankles.

Heart Weight, 240 gm. There was a small amount of pericardial fluid. The right ventricle and auricle were slightly dilated and there was a small milk patch at the apex of the left ventricle. Two small yellow plaques were seen near the origin of the descending branch of the left coronary artery.

Aorta Showed slight atheroma.

Lungs Weight, right 550 gm, left 520 gm. There was much congestion, with frank oedema in the lower lobes and frothy blood-stained fluid in the main bronchi. In the right pleural cavity there was an effusion of about 150 c c of clear fluid, but the left pleural space was empty. The hilar lymphnodes were slightly enlarged, soft, and oedematous. There was no sign of tuberculosis.

Liver Weight, 1,500 gm (Plate 11, Fig 1). This organ was extremely distorted. Most of the right lobe was converted into a mass of smooth, greenish nodules varying in diameter from one to five cm and separated by deep pits and grooves lined by greyish fibrous tissue. The left lobe was relatively less reduced in size and contained numerous similar nodules, not so uniformly distributed as in the right lobe. A large yellowish nodule, medial to the gall-bladder and compressing it, showed on section indefinite yellowish tissue suggestive of carcinoma. The great omentum was adherent to the inferior surface of the right lobe. The liver substance was of irregular consistency, some areas being tough and others soft. The predominant colour was green mottled with yellow. The blood-vessels were not prominent nor were the bile ducts dilated. The walls of the gall-bladder were thickened and white and its cavity was reduced to a narrow space containing a little thick green bile. The bile-ducts appeared normal, but the middle third of the common bile-duct had many adhesions around it as well as a leash of varicose veins communicating with the portal vein. The last was greatly distended, with a soft friable ante-mortem thrombus adherent in places to the wall and filling approximately two-thirds of the lumen. The clot extended from the junction of the splenic and superior mesenteric veins to the first branches of the portal vein. The hepatic artery appeared normal.

Spleen Weight, 330 gm. This was enlarged and uniformly stippled with tiny white patches which fused to form larger irregular bluish-white areas near the upper pole. The pulp was dark red and firm. The Malpighian bodies were very small and poorly defined. The vessels appeared normal.

Kidneys Weight, 360 gm. These were normally situated and slightly enlarged. The capsule stripped easily, disclosing a pale smooth surface with prominent stellate veins. The cortex was broad and pale, but the details were apparent, and there was a clear demarcation from the medulla. The pyramids were congested and the vessels in the walls of the pelvis were prominent. Elsewhere the renal vascular system appeared normal. The peripelvic fat was not increased in amount, and the papillae, calyces, and ureters were normal. The trigonal muscle of the bladder was rather prominent.

Genitalia The only abnormality was the very small size of the epididymes and a moderate reduction in size of the testes, which appeared otherwise normal.

Alimentary canal The tongue was small and apparently fibrotic. The mouth, nasopharynx, and tonsils were otherwise normal. In the lower half

of the oesophagus there were huge varicosities, and erosion of one of these had occurred at the cardia with haemorrhage. The stomach was small and contained prominent submucosal veins. There were a few small erosions in the fundus, and near the cardia there had been recent haemorrhage from a larger varicose vein. The pylorus and duodenum were normal, but the rest of the small intestine had a thick, greyish, rubbery wall. The large intestine was greatly distended with gas but otherwise normal. The mesenteric lymphnodes were pale and firm. The veins of the mesentery and retroperitoneal tissue were congested. The arteries were normal.

Endocrine glands Pituitary normal. Thyroid small, very pale, firm, but showed no cysts or nodules. Parathyroids not obviously enlarged. Adrenals narrow but otherwise normal. Thymus, no remnants found.

Brain Normal.

Lymphoid system There was no enlargement of the lymphnodes, which were pale and rather firm.

Bones There was no abnormality in shape of the cranial bones, but they were so thin as to be almost transparent in some areas, especially over the vault. These patches were circular with well-defined margins and 1.0 to 1.5 cm in diameter. The diploe contained little marrow, yet the bone was soft and could easily be cut with a knife. The ribs were soft, containing much spongy bone, and were more bowed than normal. There was no beading and no apparent fractures. The spine was both kyphotic and scoliotic, and the lower lumbar vertebrae were noted to be rather soft. The femora were bowed laterally and there was a slight genu valgum deformity. Osteotomy scars were present above the medial condyles. There was no enlargement of the epiphyseal ends. The femoral neck was narrow with a varus deformity. The whole bone felt very light and there was, in fact, great reduction in the cortical bone, especially in the lower third. The wide medullary cavity contained reddish-yellow marrow in the upper two thirds and yellow marrow in the lower third.

Histology Liver There was considerable thickening of the capsule, from which fibrous bands extended into the liver substance. At places within the capsule there were nodules of carcinoma which were almost certainly part of a malignant hepatoma. Within the substance of the liver, and particularly in the fibrous strands, extensive infiltrations of the carcinoma were seen, and in the intervening compressed liver tissue there was evidence of biliary obstruction. In other areas there was recent centrilobular necrosis with a focal distribution (Plate 11, Fig 2). Near the necrotic areas there was recent extensive infiltration with leucocytes, mostly polymorphonuclear cells, and at the periphery there were signs of active regeneration. In areas of normal-looking liver cells there were a number of large pale intranuclear inclusions, often seen to be lying beside the nucleolus (Plate 12, Fig 3). These intranuclear vacuoles did not stain as fat with Scharlach R, nor did they stain with Best's carmine, although the specimen was not fresh enough to be able to exclude the original presence of glycogen within them.² Similar inclusions were seen in a liver biopsy performed by Dr Sheila Sherlock six months before the patient's death.

Kidney The most marked changes consisted of swelling and vacuolation of the epithelium of the proximal convoluted tubules, whereas the distal tubules were notable for the abnormal flattening of their epithelial cells with

² It is in fact, virtually certain (Chipp and Duff, 1942) that such liver cell nuclear inclusions always do signify glycogen, and according to Warren (1938) the amount of glycogen in the nucleus varies inversely with that in the cytoplasm of the liver cells.

consequent increase in the size of the lumen (Plate 12, Fig 4) Staining with Scharlach R showed that there was a small amount of lipid in the proximal convoluted tubules, the loops of Henle, and the collecting ducts Within the tubules, especially the loops of Henle, there was granular debris and occasional granular casts The glomeruli showed little change except for slight periglomerular fibrosis, especially in the subcapsular zone A few glomeruli also showed slight swelling of the capsular epithelium and a little proliferation of the cells of Bowman's capsule The interstitial tissue was unevenly infiltrated by the strands of fibrous tissue, which were most marked in the subcapsular zone Alcohol-fixed sections were stained to show the presence of phosphatase by Gomori's (1939) method (Plate 12, Figs 5 and 6) The result was striking in that the phosphatase was demonstrated only in the loops of Henle and the collecting tubules, whereas normally it is the proximal convoluted tubules alone which contain it As a control a section of the same kidney was similarly stained, but without the addition of any potentially insoluble metallic ion, so as to show any calcium deposits, which would have given a false positive result as to the presence of phosphatase This control was negative

Analysis of organs Chemical tests for cystine in the liver and spleen were negative Analysis of the liver gave the following composition by weight

Water	78.9 per cent
Protein	14.3 per cent
Fat	3 per cent
Undetermined	3.8 per cent

The protein figure was derived from a Kjeldahl nitrogen result of 2.48 per cent As the non-protein nitrogen is very constant at approximately 0.2 per cent the protein nitrogen was assumed to be 2.28 per cent Therefore the percentage of protein (nitrogen $\times 6.23$) is 14.3

In the absence of a fuller knowledge of these values in normals and in cases with necrosis of the liver it is not possible to interpret the above results adequately, but in rats similar figures would indicate a higher water and lower protein content than normal This suggests that some degeneration of liver cells was taking place (Himsworth and Glynn, 1945)

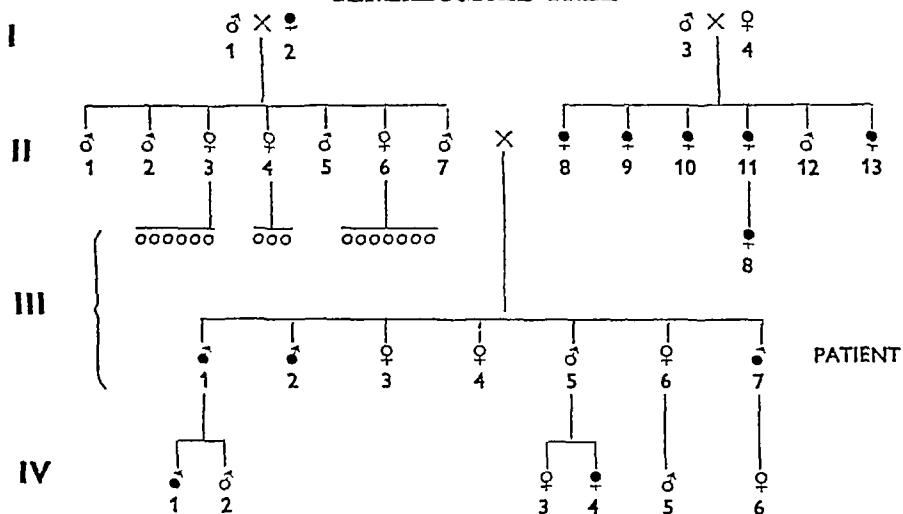
Analysis of skull A piece of dry, fat-free bone from the skull was analysed The nitrogen content, the weight of ash on direct ignition, and the calcium phosphate were all within normal limits, and there is therefore no suggestion that the bone was in any way abnormal in its chemical composition

Heredity

The striking feature in the family history of our case is the high incidence of one or more features of the Fanconi syndrome in the patient's mother and four maternal aunts, all of whom were so affected This could be interpreted as being due to a homozygous recessive gene producing the syndrome in this generation In favour of such a view is the fairly frequent finding of consanguinity in other reported cases of the syndrome (McCune, Mason, and Clarke, 1943) There are, however, at least two reasons for not accepting this explanation Firstly, it would necessitate postulating that the same recessive gene was provided by the patient's father in order to account for the development of the syndrome in the patient Such a second successive chance occurrence of a gene, which must be very rare judging by the

infrequency of the Fanconi syndrome, would be intrinsically unlikely. Secondly, the presence of such varied features of the syndrome in his aunts does not suggest that the affected members of this generation were homozygous

GENEALOGICAL TREE



II 6, 8, 13 } were examined and their urine tested In no case was any albumen
 III 1, 2, 3, 4, 6 } or abnormal amount of cystine found, and II 13 was the only one to
 IV 5, 6 } have glycosuria

INCIDENCE OF BONE DEFORMITY, GLYCOSURIA, AND HEPATOMEGALY

(Shaded symbols in the above table)

- I 2 Possibly had diabetes
- II 8 Deformity of back, hips, and lower limbs with shortening of stature Hepatomegaly X-rays suggestive of advanced Paget's disease
- 9 Deformity of back and hip Investigated as case of possible hyperparathyroidism Probable hepatomegaly Urinary gravel
- 10 Glycosuria not requiring insulin
- 11 Glycosuria requiring insulin Gangrene of foot
- 13 Glycosuria shown to be renal in type
- III 1 Deformed foot and arthritis of hip, probably due to old poliomyelitis
- 2 Spontaneous fracture of patella
- 7 The patient
- 8 Deformity of leg
- IV 1 } Slight genu valgum
- 4 }

with respect to the Fanconi syndrome. It is consistent with these sisters being heterozygous and the condition being due to an irregularly dominant gene. Other indirect evidence for this may be adduced by a consideration of the age factor in the incidence of the syndrome. There are 17 cases among McCune, Mason, and Clarke's collection, in addition to our own, which had no known defect of cystine metabolism. In 14 of these the first symptoms of the syndrome were noticed at between two months and four years of age, and in the remaining three at 21, 30, and 31 years, although two of these patients had had rickets as children. There thus appear to be two age groups

at which the syndrome may be manifested, and it is suggested that these age groups may have different genetic characteristics. If the gene producing the syndrome were a dominant, then the homozygotes might be expected to develop the characteristic disturbances in the first few years of life, or die *in utero*, whereas heterozygotes might have a more insidiously developing and variable disease picture. Thus would be explained the irregular incidence of one or more features of the syndrome in the adult blood relatives of our patient. The familial incidence of our case is best explained by postulating the presence of a dominant gene with the occurrence of irregular dominance, whereas other recorded cases in which consanguinity has been noted are far more likely to be due to a recessive gene. A recessive type of inheritance is also suggested by the low familial incidence of the syndrome in McCune, Mason, and Clarke's cases without cystinosis. There is only one report of familial incidence and this in a sibling from among 16 such cases, and there are at least three instances of consanguinity, an incidence some 14 times greater than in the general hospital population (Bell, 1940). It is of interest that consanguinity was not noted in the two adult cases included, nor was it discovered in our adult case. It therefore seems possible that there are two allelomorphs which may produce the Fanconi syndrome, a dominant appearing in adults and a recessive in young children. Another feature of the family history of our case is that the only person not affected among the patient's mother and her five siblings was the patient's uncle. The question of sex-linkage should therefore be considered. Since so many of this generation were affected, a sex-linked gene would almost certainly be a dominant and, if this were true, the patient's daughter would show signs of the syndrome. This was not so, at least up to the age of nine years, and thus the theory of sex-linkage lacks support.

Since renal glycosuria is a feature of the Fanconi syndrome, and cystinuria may also be one, it is interesting to note that the former is thought to be inherited as a monofactorial dominant character (Hjarne, 1927, Babson, 1940) and the latter as a recessive, possibly depending on more than one gene (Garrod, 1923, Thin, 1929). When renal glycosuria and cystinuria are studied separately it is apparent that they are not well developed single disturbances, hereditary cystinuria may, for instance, be associated with the presence of various other amino-acids in the urine (Garrod, 1923, McLester, 1935), and an example of the Fanconi syndrome has recently been described with true diabetic glycosuria (Aidin and Nobel, 1942), whereas glycosuria may appear with abnormal frequency in families having a high incidence of osteoporosis and Paget's disease (Moehlig, 1936). The impression to be gained from such a diversity of individual features tending to show a hereditary transmission in various combinations is that there may be modifying genes playing an important subsidiary role in altering the manifestations of the determining dominant or recessive genes. (The genetic interpretation given in this section was made after consultation with Professor L. S. Penrose.)

Discussion

Summarizing the many aspects of this complicated but typical case we have a 35-year-old man with severe osteomalacia occurring in the absence of a dietary deficiency of vitamin D. Although the renal function was moderately impaired, the blood-urea was normal and the serum inorganic phosphorus conspicuously low. The osteomalacia was therefore not due to hyperparathyroidism secondary to renal failure. There was an excess of unidentified acids in the blood and an associated increase of ammonia production by the kidney. Glycosuria existed in the presence of a normal blood-sugar level, and heavy amino-aciduria occurred in the presence of a normal amino-acid level. Lastly there was a nodular hyperplasia and primary carcinoma of the liver. We feel that the presence of a primary carcinoma in the liver does not invalidate our biochemical findings, since an excess of amino-acids has been found in other uncomplicated cases of the Fanconi syndrome, and in conditions of severe liver degeneration the amounts of the various amino-acids bear relation to their occurrence in liver protein.

In the condition of hyperchloraemic nephrocalcinosis there is also renal dysfunction, rarefaction of bone, and low serum-phosphate. There is, however, unlikely to be any more fundamental association between this state and the Fanconi syndrome, for the demineralization of bone in nephrocalcinosis is apparently due to loss of basic calcium ions secondary to deficient ammonia formation by the kidney, whereas in the Fanconi syndrome it appears to be due to excessive loss of acid phosphate ions. Also it has been suggested by Albright, Consolazio, Coombs, Sulkowitch, and Talbott (1940) that the hypophosphataemia in nephrocalcinosis is due to a secondary hyperparathyroidism, whereas in the Fanconi syndrome it is due to a low renal threshold for phosphates, perhaps accentuated by a slight degree of parathyroid hyperactivity (Albright, Burnett, Parson, Reifenstein, and Roos, 1946). These authors also point out in contrast that the acidosis in the Fanconi syndrome is due to an excess of acids, whereas in hyperchloraemic nephrocalcinosis, or, as they class it, tubular-insufficiency-without-glomerular-insufficiency, it is due to a decreased ability to excrete acid. There is, in fact, little difficulty in the differential diagnosis between the two conditions, especially if the characteristic high plasma-chloride and low plasma-bicarbonate of nephrocalcinosis are found (Baines, Barclay, and Cooke, 1945).

The glycosuria, amino-aciduria, and probable hyperphosphaturia of our case were presumably due to a renal tubular disturbance, since the respective blood levels were below the normal renal threshold. Hyperphosphaturia was never demonstrated in our case, although it has been a striking feature of other reported cases of this syndrome (McCune, Mason, and Clarke, 1943). Our failure to identify it may have been due to the patient having reached an equilibrium stage.

While it thus appears that the primary disturbance in the Fanconi syndrome is a failure of tubular absorption of glucose, amino-acids, and phosphates, the

cause of the tubular disturbance remains obscure. A chronic tendency to acidosis may be an important factor in lowering the renal threshold for phosphates, but a more comprehensive hypothesis follows from the finding of an atypical distribution of phosphatase in the kidney. Whereas the proximal convoluted tubules are the only sites where phosphatase may be demonstrated in a normal kidney (Gomori, 1939, Menten, Junge, and Green, 1944), these were the areas most conspicuous for its absence in the present case. Glucose and phosphate are reabsorbed in the proximal convoluted tubules (Richards, 1938), and in this connexion it is of interest that glucose is transferred across the tubular epithelium in the form of phosphate esters. Deficient phosphate absorption might therefore be expected to affect glucose absorption from the glomerular filtrate, especially if there is in addition a deficiency in tubular phosphatase. A similar explanation has been offered for the deficient glucose absorption in sprue (Maegraith, 1946). This author has suggested that deficient phosphorylation is an aetiological factor, and has shown that glucose absorption from the intestine may be increased by giving a buffered phosphate solution by mouth. In our patient there was evidence that a similar mechanism produced both the glycosuria and the amino-aciduria, since their respective daily outputs seemed to vary together. It is suggested, therefore, that all three substances, phosphate, glucose, and amino-acids, are reabsorbed mainly in the proximal convoluted tubules, and that lack of available phosphate for the phosphorylation of glucose and amino-acids may be a primary cause for their impaired reabsorption. Although amino acids are dealt with in various ways by the kidney (Smith, 1937), the hydroxy amino-acids, which are known to occur naturally as phosphoric esters, did in fact appear in relatively greater amounts in the urine.

The persistently alkaline urine of our patient is of considerable interest, especially in view of the fact that the ionic equation of the plasma showed a discrepancy with an excess of cations totalling 20 meq, not more than 12 of which could be attributed to combined analytical error. Unidentified acids must therefore have neutralized at least some of the excess cation. These unidentified acids were in turn more than neutralized in the urine, and it was therefore not surprising to find that the ammonia coefficient of the urine was two to five times normal. McCune, Mason, and Clarke (1943) have produced figures for the organic acid excretion in the urine of a child with the Fanconi syndrome. They found the surprisingly high daily excretion of 100 to 150 meq and claimed that 82 per cent of this represented amino-acids. However, their analytical methods are not above question, as they appear to have determined both aliphatic organic acids and amino-acids together by the method of Van Slyke and Palmer (1920). This method is not applicable to the determination of amino-acids, or of organic acids in the presence of excess amino-acids. If the increase in acids in the plasma is regarded as a primary abnormality, there could be said to be a tendency to chronic acidosis. Such a state is known to cause hyperphosphaturia in both animals and man, changes even within the physiological range of blood pH producing quite marked differences

in phosphate output (Haldane, Wigglesworth, and Woodrow, 1924, Guest and Rapoport, 1940, Boyd and Stearns, 1941, Harrison and Harrison, 1941) Chronic hyperphosphaturia leads to loss of phosphate, and with it calcium, from bone, so that finally a state of osteomalacia is produced. In the Fanconi syndrome, therefore, there may be two factors in the development of hyperphosphaturia, namely chronic mild acidosis and a low renal threshold for phosphate, the former possibly contributing to the latter. The persistent alkalinity of the urine may have been important in the development of some of the renal histological lesions. The evidence for this is no more than suggestive and is based on the work of Lowenhaupt and Greenberg (1946) with rats maintained on a chloride-deficient diet. The chronic alkalosis so produced was associated with degeneration of the renal tubular epithelium and loss of alkaline phosphatase from the proximal convoluted tubules, both being similar to the changes in our case. In addition the rat kidneys had calcium deposited in the lumina of the collecting tubules. Somewhat similar lesions have been noted by Morehead, Fishman, and Artom (1946) working with rats on a diet containing an excess of serine, an amino-acid which appeared in abnormally large amounts in the urine of our case.

Damage to the liver is not an invariable feature of the Fanconi syndrome, as is shown by consideration of the 39 cases collected by McCune, Mason, and Clarke (1943), autopsies were carried out on 12 of these, and in five the liver was reported as being normal. The seven abnormal cases comprised four with focal necrosis, two with cirrhosis, and one with fatty infiltration. These figures are inconclusive, but they suggest that the presence of an abnormal liver is more than a coincidence. Himsworth and Glynn (1944*a, b*) have shown that rats on a diet deficient in methionine and cystine develop a trophopathic cirrhosis. Methionine and cystine, however, were among the few amino-acids which were not excreted in excess in the urine of our patient, so that despite the amino-aciduria a primary deficiency of these acids was unlikely to be the cause of the liver changes. The question of a possible abnormality in their endogenous metabolism was then considered. For instance it is known that cystine is formed in the body by the combination of serine, which supplies the carbon chain, with sulphur derived from methionine. If then cystine synthesis were impaired, an excess of serine might be expected to appear in the urine, as it did in our case. Other short-chain amino-acids such as glycine and alanine could also have been derived from cystine or methionine. If the excessive loss of serine indicated a deficient cystine synthesis, one might have expected a corresponding urinary loss of sulphur, but the results of the studies in sulphur metabolism were entirely normal. A primary disturbance of the amino-acid metabolism also could not explain the excess of other amino acids in the urine. The theory that the cirrhosis was due to amino-acid deficiency could not therefore be sustained. In some other reported cases of the Fanconi syndrome, apparently indistinguishable clinically from our own, pathological deposits of cystine have been present in the tissues (Lignac, 1924, 1938, Russell and Barrie, 1936), and sometimes

there has been cystinuria as well (Lignac, 1924, Pache, 1940) It has been suggested that the cystine crystals in the liver may have provided a mechanical cause for the cirrhosis (McCune, Mason, and Clarke, 1943), but the other features are not so readily attributable to the cystinosis. Curtis and Newburgh (1927) and Gyorgy and Goldblatt (1942) have, however, noted lesions in the kidneys as well as in the livers of rats (Earle and Victor, 1941) which had been fed with 5 to 10 per cent of cystine in the diet. If the defect in human cases of cystinosis were an impairment of the breakdown of cystine, leading to its accumulation in the body, they might be considered comparable to Gyorgy and Goldblatt's rats. This theory of deficient cystine breakdown would need further to postulate that the excess cystine had a selective effect on the kidney tubules, rendering them less able to reabsorb glucose, amino-acids, and phosphates. No abnormality of cystine metabolism was, however, found in our patient, so this explanation is untenable.

We must, therefore, admit that no satisfactory explanation has as yet been advanced to explain the occurrence of hepatic lesions in the Fanconi syndrome. All that can be said is that the lesion closely resembles that produced in animals by a deficiency of certain amino-acids, and we would point out that the Fanconi syndrome is the only known disease in which persistent amino-aciduria occurs.

Quite apart from any change in kidney phosphatase, pathological changes have been described in the structure and appearance of the renal tubules (McCune, Mason, and Clarke, 1943). The types of change are remarkably inconstant and include flattening of the tubular epithelium (van Creveld, 1934), deposit of fat in the basal stratum of the proximal convoluted tubules (Fanconi, 1936), marked swelling of the tubular epithelium (Guild), particulate matter which may have been cystine deposited in the tubule cells (Lignac, 1924, Fanconi, 1931, Beumer and Wepler, 1937), and in one case a remarkable uneven fibrosis as well (Russell and Barrie, 1936). In McCune, Mason, and Clarke's review there is only one autopsy report which does not describe renal tubular lesions from among 10 reports on autopsies performed on cases with rickets and glycosuria. The fact that our case showed tubular flattening in some places, swelling of the tubular epithelium with fatty change in other places, and also an abnormal degree of fibrosis would be consistent with the view that these varied changes may represent different phases of development of one process rather than separate entities.

Summary

- 1 A case of the Fanconi syndrome is reported in a 35-year-old man. The syndrome was characterized by severe osteomalacia, mild diabetes with an added renal glycosuria, amino-aciduria, hypophosphataemia, and fibrosis of the liver with a terminal primary carcinoma of this organ.

- 2 Special studies were made of the amino-acid and sulphur metabolism, the ionic equilibrium of the serum and urine, and the hereditary aspects. No abnormality of the metabolism of the sulphur-containing amino-acids

was discovered, although this has been a feature of some other reported cases of the syndrome. The heredity in our case was consistent with the transmission of a mendelian dominant gene responsible for the syndrome. In other cases occurring in children there is strong evidence for a recessive type of heredity.

3 Factors in the pathogenesis of the syndrome were thought to be an incompetence of the renal tubules to reabsorb glucose, amino-acids, and phosphates, with a tendency to chronic acidosis. Histochemical methods provided evidence for a deficient phosphorylation mechanism in the proximal convoluted tubules. Suggestions are made as to the normal mechanism of reabsorption of these substances in the renal tubules.

Grateful acknowledgment of assistance is made to Professor H P Hims-worth, Professor G R Cameron, Professor L S Penrose, Dr M Maizels, Dr M. Rosenheim, and Dr L E Glynn.

Appendix on Methods

Prothrombin index Innes and Davidson (1941)
 Blood-urea by urease method
 Blood-cholesterol by Liebermann-Burchard acetic anhydride method
 Serum and urinary calcium Kramer and Tisdall's method (Tisdall, 1928)
 Alkaline phosphatase King and Armstrong (1934)
 Serum and urinary phosphorus Youngburg and Youngburg (1930)
 Serum protein by Kjeldahl method
 Serum chloride Peters and Van Slyke (1932)
 Serum bicarbonate Maizels, McArthur, and Payne (1930)
 Serum and urinary sodium McCance and Shipp (1931)
 Serum and urinary potassium Jacobs and Hoffman (1931)
 Serum and urinary magnesium Denis (1922)
 Urinary chloride by Volhard-Arnold method
 Urinary protein by sulphosalicylic acid method
 Urinary sulphate by Folin's method
 Urinary ammonium Malfatti (1908)
 Urinary pH by colorimetric method with B D H capillators

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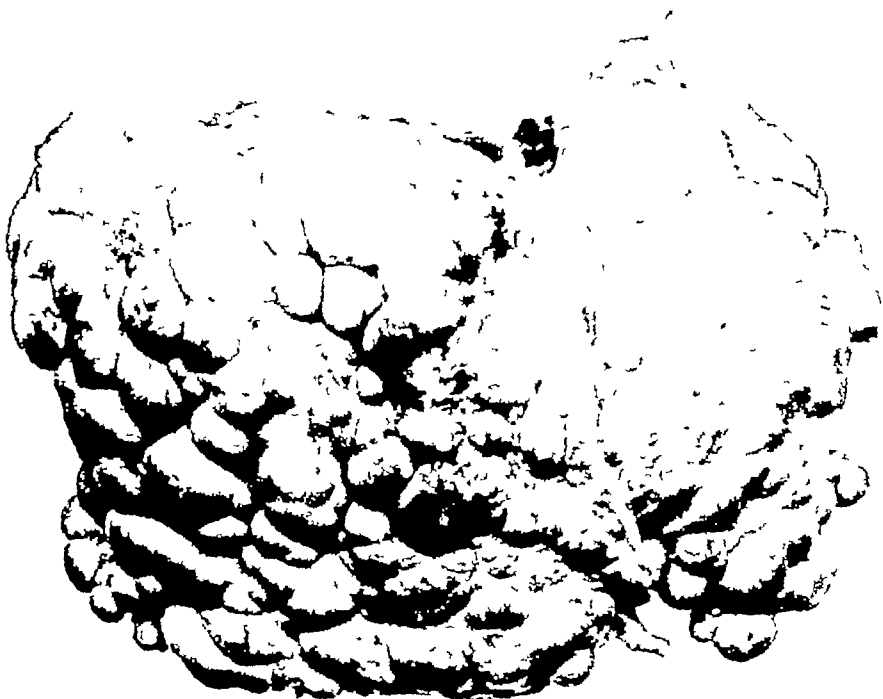


FIG. 1 Liver showing marked nodular hyperplasia

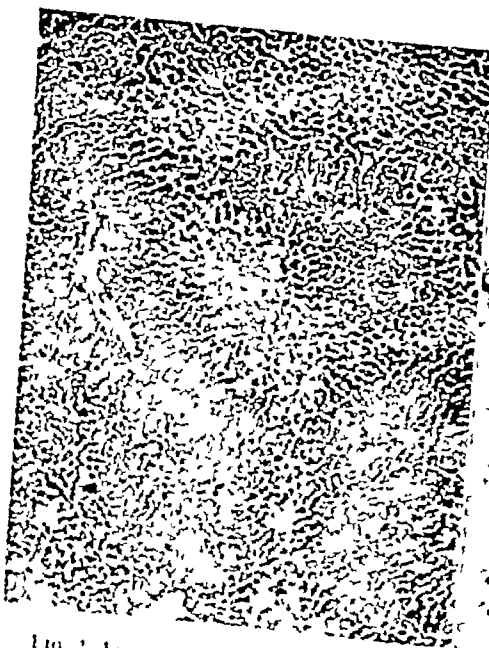


FIG. 2 Liver (haematoxylin and eosin) centrilobular necrosis



FIG. 3 Liver (haematoxylin and eosin) intranuclear vacuole

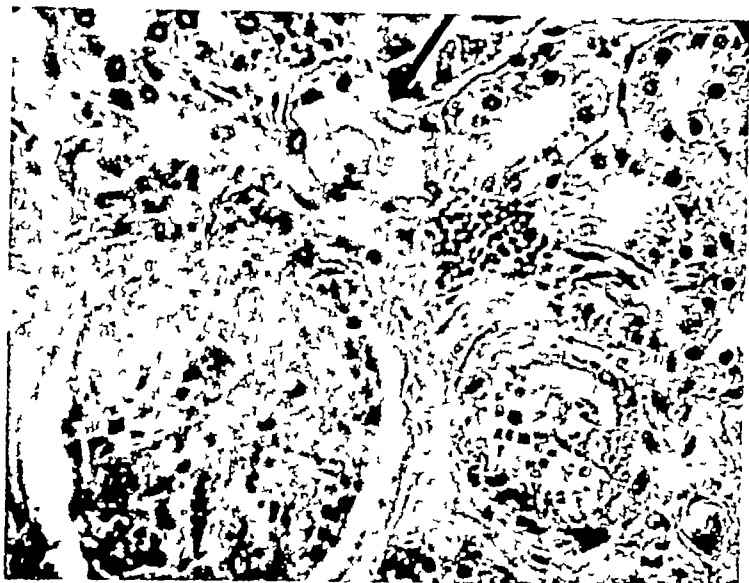


FIG 4 Kidney (haematoxylin and eosin) showing flattening of the epithelial lining of a distal tubule



FIG 5 Normal kidney (Gomori's phosphatase stain and neutral red) Only the proximal tubules have taken up the phosphatase stain

FIG 6 Kidney of our Case (Gomori's phosphatase stain and neutral red) The phosphatase is shown only in the collecting tubules and Henle's loops

SNAKE-BITE BY *ECHIS CARINATA*¹

By R. H. MOLE AND ANGUS EVERARD

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ECHIS CARINATA, the saw-scaled viper, is found in sandy desert countries. Very diverse opinions are expressed on the seriousness of its bite. Taylor and Mallick (1935*b*) considered that death is uncommon because the *Echis* is not specially aggressive and, being small even when full-grown, can inject little venom. Purohit (1944), on the other hand, stated that the inhabitants of Jodhpur, India, consider it by far the most poisonous snake in their neighbourhood, and similar differences of opinion are recorded by Corkhill (1932*a*) and Gharpurey (1931). Clinical accounts of *Echis*-bites are uncommon and usually incomplete because a trained observer is rarely near when the patient is bitten. Fifteen cases have been found in the literature of the last 30 years, 11 from India (Wall, 1913, Chuhan Singh, 1924, 1925*a, b*, Gharpurey, 1931, Robertson, 1935, Purohit, 1944), and four from Iraq (Corkhill, 1932*a*). Pain, swelling, and extravasation of blood occur at the site of the lesion as with all viperine-bites. Between six and 36 hours after the bite generalized bleeding begins from gums and intestine, into the urinary tract, from the skin lesions, and even from the conjunctivae. The haemorrhages continue for three or four days or even longer, and may be sufficient to produce a severe anaemia as in Robertson's (1935) case where the red-cell count on the fifth day was 1,600,000 per c mm. Taylor and Mallick (1935*b*) described the post-mortem findings in monkeys injected with *Echis* venom. The main feature was haemorrhage in many organs, specially the lungs. Taylor, Mallick, and Ahuja (1935) recorded that the blood loses its ability to clot *in vitro* in fatal cases, and for a time in some monkeys which received a sublethal dose. This failure to clot was shown to be the result of the absence of fibrinogen (Taylor, Mallick, and Ahuja, 1935). Two cases of *Echis*-bite in British soldiers are recorded in the present paper. The first man did not receive any early treatment and his subsequent illness was extremely severe. His blood contained hardly any fibrinogen or platelets, and in addition he showed a disturbance of liver function lasting for many weeks. The second case, as a result of efficient and early treatment, showed none of the usual systemic effects of snake-bite. Nevertheless he, too, had a marked thrombocytopenia and a disturbed liver function like the first case, but less in degree.

Case Reports

Case I On the night of July 31–August 1, 1945, a private soldier, aged 25 years, was returning to his billet about midnight by a short-cut through

¹ Received April 14, 1947

the desert scrub Suddenly he felt a pain in his right ankle 'like two red-hot needles' Looking down he saw a small snake about 18 in long scurry off into the undergrowth He reached his billet in a few moments and with the help of another soldier incised the area of the bite with a razor blade until it bled freely The pain in the leg was severe enough to keep him awake through the night He vomited and defaecated frequently and developed a severe thirst Some eight and a half hours after the bite he reported sick and was sent into hospital On arrival his general condition

TABLE I

Day of illness	2	3	6	9	15	27
Haemoglobin (%N P L standard)	90	70	75	80	90	110
White cells (per c mm)	16,000	19,000	14,000	8,000	10,000	—
Neutrophils (per c mm)	15,000	17,000	12,000	6,000	—	—
Platelets (per c mm)	Too few to count	Too few to count	30,000	140,000	330,000	200,000
Plasma fibrinogen (mg per 100 c c)	<10	<10	70	120	250	—
Clotting time of venous blood (Lee and White) in minutes	90	12	9	6	6	7
Quality of clot	A few tiny fibrin strands only	Small and poor	Not firm	Normally firm and retractile	Normal	Normal
Icteric index	11	—	22	12	12	5

was fair, but he was restless and slightly confused mentally so that it was possible to doubt the accuracy of his history The temperature was 99.8° F, pulse 86, and respiration 18 The right foot and leg up to the knee were swollen and patchily discoloured by extravasated blood The foot was quite cold and the popliteal pulse not palpable The toes and foot could scarcely be moved by the patient, and skin sensation was lost over the swollen area

Initial treatment Soon after the patient was put to bed, and some 11 hours after the bite an intravenous injection of concentrated polyvalent anti-venom serum (Kasauli) was begun When 5 c c had been given the patient became restless and then collapsed He was cold, cyanotic, sweating profusely, and his pulse was barely perceptible The serum injection was stopped, adrenalin given, and recovery followed Later, 20 c c of 10 per cent calcium gluconate was administered intramuscularly and the patient was placed in an air-conditioned room Local treatment was confined to elevation of the leg, sulphonamide powder to the region of the bite, and cold packs A hand-fan played a current of air on to the wet packs to augment the cooling effect

Subsequent course During the afternoon and night the patient's general condition deteriorated He became increasingly restless and confused, and took fluids with difficulty due to persistent nausea and retching His pulse-rate fluctuated irregularly between 68 and 120 At midnight blood began to ooze from the foot and from the sites of intravenous and intramuscular injections At 2 a.m. small blisters were beginning to appear on the right foot At 4 a.m. 420 c c of heavily blood-stained urine were passed, the first urine since admission At 5.30 a.m. his vomit was noticed to be streaked with blood On the second day his condition was serious Haemorrhage continued and the pulse-rate fluctuated The blood-pressure was 110/80 The foot and leg were more discoloured and the swelling had increased and spread up into the thigh The blisters on the foot were larger Coldness

and pulselessness of the foot persisted and a surgical opinion was sought on the advisability of amputation in view of the probability that gangrene was already occurring and that the wound site at least was infected. It was considered by S/Ldr Sawyer that the patient was unlikely to survive operation and that the correct treatment was expectant. At midday on the second day a blood-count and other investigations were carried out (Table I)

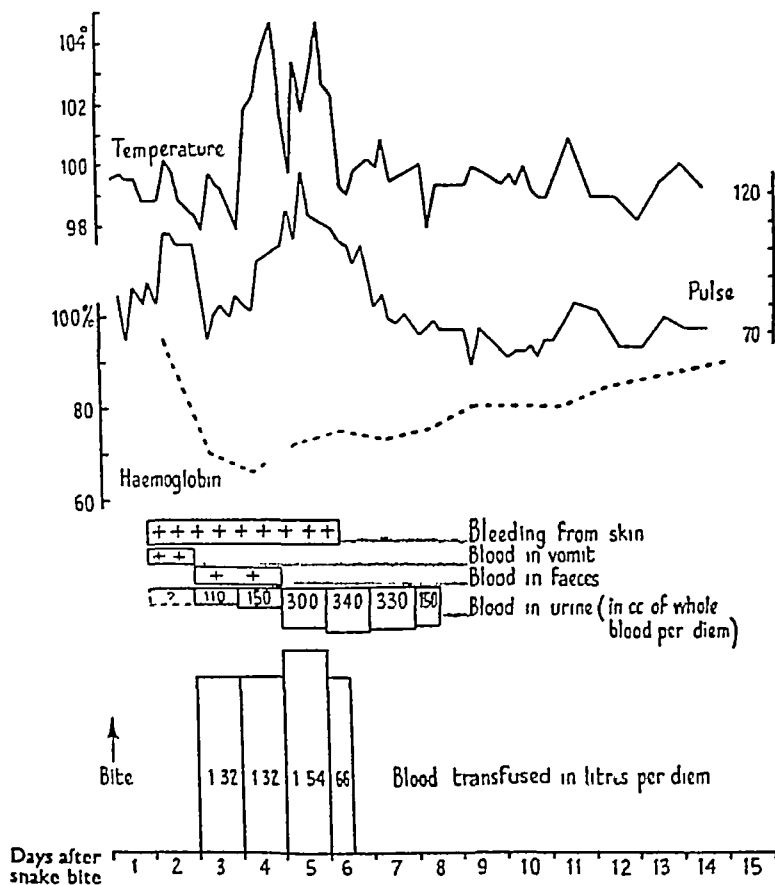


FIG 1

Venous blood was quite fluid at 37°C until between one and two hours after the specimen was taken, when a few tiny strands of fibrin could be seen. In view of the continued haemorrhages, the absence of platelets, and the failure of the blood to clot, it was decided to transfuse the patient with freshly drawn citrated blood. A long-continued transfusion was in prospect and it was decided to use blood of homologous group only, even though the patient's Group was B. Cross-matching of the patient's serum and donors' red cells was carried out in tubes at 37°C. Finding Group B donors without a history of malaria and having to cut down on a vein in the left foot and tie in a cannula delayed the administration of blood till about midnight, 48 hours after the snake-bite. After 12 hours, during which saline and two bottles of blood were given intravenously and fluids were forced by mouth, there was definite clinical improvement (third day). The pulse-rate dropped to 75 and

was much more steady (Fig 1) The right leg was a little warmer, but haemorrhages were continuing as before, and extravasated blood had spread high up the thigh Subcutaneous ecchymoses were appearing at pressure points and the patient produced a liquid stool containing much blood This stool and the urine specimens passed on this and succeeding days had a marked ammoniacal smell The haemoglobin level had dropped 26 per cent since the previous day The fourth and fifth days were the period of greatest anxiety, although on the fourth day the circulation was clearly being re-established in the right leg The haemorrhages from the various skin lesions and into the urine became increasingly profuse (Fig 1) Blood was seeping subcutaneously round the venepuncture sites as well as soaking into the dressings The pulse-rate and temperature were rising (Fig 1) The haemoglobin at first fell further and the platelets were still almost absent (Table 1) On the morning of the fifth day the patient suddenly turned pale and became extremely restless and delirious for a few hours The pulse rose abruptly to 130, and the blood-pressure was 140/55 At the time a pulmonary embolism consequent on the improved circulation through the right leg seemed the likely cause, although an X-ray of the chest on the tenth day showed no evidence of a pulmonary infarct During the fifth night the patient was irrational and picking at his bed-clothes On two occasions his limbs and trunk went into spasm in extension, and later he had a delirious attack similar to the one that he had had earlier in the day, but of shorter duration On the morning of the sixth day his general condition improved and became fairly good At 11 o'clock it was noticed that all bleeding from the skin had suddenly stopped within the previous three hours He produced a small faecal stool without any obvious signs of blood in it At midday the transfusion was terminated because all bleeding, except into the urine, had ceased and because all 11 suitable Group B donors in the district had been utilized The haemoglobin was then 75 per cent Blood continued to appear in the urine in increasing concentration until the morning of the eighth day Nevertheless, by the evening of that day the urine was clear of blood to the naked eye Again it was surprising how abruptly the haemorrhage ceased

Convalescence Once the circulation through the right leg and foot was well re-established there occurred a rapid reduction in the tenseness of the swelling and the grossest pitting oedema became demonstrable By the sixth day joint movements were full and the patient was allowed up in the belief that movement of the affected leg would accelerate repair On the seventh, tenth, and eleventh nights the patient was incontinent of urine Recovery was very slow Nothing was obviously the matter with the patient, but he was lethargic and lifeless in his attitude and behaviour, and his appetite was poor Five weeks after the bite he had a transient acute tonsillitis with fever up to 103° F A fortnight later he was noticed by the nursing staff to be rather strange in manner and during the night he was confused and very apprehensive He had gone to bed reluctantly and refused sedatives The next day he would not eat or drink, finally declaring that people were trying to poison him He thought that his cigarettes were poisoned and that other patients were against him because they did not speak to him Actually during the preceding weeks he had been the object of a good deal of attention and had had many visitors from his battalion, for the drama of his illness had spread abroad At first he was considered to be schizophrenic, but later developed a good deal of insight and was invalided home to the United Kingdom in November with the psychiatric diagnosis of a mild paranoid state His physical condition was then better than at any other

time in hospital, but he still did not seem to have fully recovered his normal health. He gave a history of always feeling inferior to his younger brother and sister, and of shyness and difficulty in making friends. His father had long been prone to irritable fatigue states, and his mother suffered from 'indigestion due to her nerves'. His sister had nervous dyspepsia too. On arrival in the United Kingdom he had to be admitted to a military asylum where he still was a year afterwards.

Identity of the snake The commonest poisonous snake in this area of Sind is the saw-scaled viper *Echis carinata*, and this is much the most likely snake to have bitten the patient. His description of the snake's size agrees, and the fang-marks which could be seen on the foot after the swelling had subsided were then less than one inch apart. An attempt was made to prove the identity of the snake by demonstrating a specific anti-venin in the patient's serum, but without success. The patient's melaena is also of significance, since Corkhill (1932*b*) stated that he was 'unable to find any record of melaena in a case of snake-bite in any instances other than those in which the snake concerned was *E. carinatus*'.

Laboratory investigations Repeated haematological examinations were carried out and are summarized in Table I. Fibrinogen was estimated gravimetrically at the time, but the clots were preserved and the estimates checked by digestion and Nesslerization. The method of Macfarlane (1937) was used in a search for a fibrinolysin. No fibrinolytic activity could be demonstrated in blood taken on the second and sixth day. Serum from these samples did not delay the coagulation of recalcified oxalated normal plasma, so that anticoagulant activity appeared to be absent also. The bleeding time (Duke) on the fifth day was 4 min (normal up to 3 min). The white-cell counts are given in Table I. Lymphocytes, monocytes, and eosinophils were present throughout in normal numbers. Cooke-Ponder counts of the neutrophil granulocytes were as follows:

Day	5	6	8	10	12
Neutrophil granulocytes (per c mm)	13,000	12,000	5,200	6,100	6,200
Percentage distribution of granulocytes					
Lobes { one	72	54	34	18	16
two	21	42	44	40	36
three	7	4	16	32	36
four or more	—	—	6	10	12

Reticuloocytes were counted daily from the seventh to the fifteenth day. The values were 0.5, 0.5, 0.5, 2, 2.5, 3, 1, 2, and 1 per cent respectively. Nucleated red cells were seen in the peripheral blood only on the fifth day when there were occasional orthochromic normoblasts. The blood-urea on the sixth day was 60 mg and on the ninth day 40 mg per 100 c.c. After the second day all specimens of urine were saved and their volume and haemoglobin-content determined. The daily values for blood-loss in the urine are given in Fig. 1, expressed as c.c. of blood containing 100 per cent of haemoglobin. Urinary 'ammonia' was determined by formol titration. The results were inexact because the pigment in the centrifuged supernatant fluid made the determination of the end point of titration difficult. On the fifth day the ammonia concentration was as high as 0.35 gm. per 100 c.c. in one specimen and the total excreted in 18 hours was 5.8 gm. Hippuric acid excretion was measured after oral ingestion of 4 gm. of sodium benzoate.

The determinations of hippuric acid in urine were made by the method of Weichselbaum and Probst (1938). The results are given in Table II. Bacterial culture of fluid from a blister on the right foot on the fourth day yielded a pure growth of *Staphylococcus aureus*.

Case 2 On 28.5.46, at 9.50 p.m., a gunner put his right hand under the bench on which he was sitting and felt something moving. He tried to squash it, but felt a violent pain in his right thumb. He snatched the hand away and as he raised it from under the bench a snake was seen suspended

TABLE II

Sodium Benzoate Detoxication Tests

Case 1	Day of illness	21	43	73
	First two hours	17	27	47
	Second two hours	33	40	45
	Total in four hours	50	67	92
Case 2	Day of illness	3	9	20
	First two hours	30	40	41
	Second two hours	27	43	41
	Total in four hours	57	83	82

The amount of hippuric acid excreted was converted to sodium benzoate and expressed as a percentage of the oral dose of benzoate.

from the thumb into which its fangs were fixed. The snake was killed at once and later identified as an *Echis carinata* not yet fully grown. Within 15 min. the bite had been incised till it was bleeding freely and an intermittent tourniquet applied to the arm. Within three-quarters of an hour 10 c.c. of polyvalent anti-venin (?Haffkine) had been given intravenously. On arrival at hospital a little later the patient's general condition was good and there was no swelling of the bitten thumb. Five hours after the bite he complained of abdominal pain and retching. A further 10 c.c. of anti-venin (Haffkine) was given intravenously and advantage taken of the venepuncture to start haematological investigations. There was no recurrence of the pain and after his disturbed night the patient slept through most of the following day. At no time were there any detectable haemorrhages or any visible lesion in the bitten thumb except the therapeutic incisions. On the third day the patient began to resent being confined to bed, yet when he was first allowed up on the sixth day, he did not in fact feel as well as he thought he would. Even after a fortnight, when the thumb wound was completely healed, he did not feel really well or as energetic as before the bite.

Laboratory investigations Six hours after the bite a blood sample was taken and contained urea 50 mg. per 100 c.c. of blood, proteins 7.2 gm. per 100 c.c. of serum, and fibrinogen 280 mg. per 100 c.c. of plasma. The icteric index was 5, haemoglobin 112 per cent, red cell 5,400,000 per c.mm., and white cell 11,000 per c.mm., with 79 per cent neutrophil polymorphonuclears. The next day the white cells were 6,000 per c.mm. At six hours blood platelets were too few to be countable. Repeated estimations were made (Fig. 2) and showed a steady rise to normal between the third and fourth days. Fourteen hours after the bite, when the platelets numbered 15,000 per c.mm., the bleeding time (Duke) was four and a half minutes, and the tourniquet test was faintly positive, about 20 small petechiae being

produced in the upper forearm by a tourniquet applied at 80 mm pressure for five minutes. Such petechiae were found not uncommonly in a series of tests on normal controls. Benzoate detoxication tests were carried out by the same technique as before and the results are given in Table II. About four litres of urine were passed in the first 24 hours in hospital because fluids were forced by mouth. Only the second and third specimens, produced during the ninth to twelfth hours after the bite, were obviously pigmented. Their combined volume was 1.5 litres and, although the specific gravity was

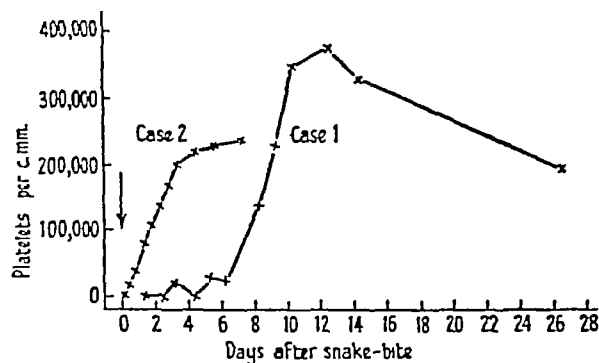


FIG 2

only 1.002, Ehrlich's test for urobilinogen was positive in a dilution of one in four.

Other cases Two other British soldiers with snake-bite as a diagnosis were admitted to the same hospital in the two summers covered by this report. There was considerable doubt about one of them ever having been bitten at all. The other had had a glancing bite over the insertion of the tendo achillis. The snake was killed and was an *Echis carinata* apparently fully-grown. This patient received early first-aid and anti-venin (Haffkine) about one and a half hours after the bite. Platelet counts at one and a half hours, four hours, and nine hours were all the same and normal. There was a marked leucocytosis of 15,000 per c.mm. with 90 per cent granulocytes at four hours. Several further cases of snake-bite, including fatal cases, presumptively due to *Echis carinata*, occurred in Indian troops in the same area, but were not observed personally.

Discussion

Snake-bite is usually considered a most uncommon accident. For instance, Corkhill (1932*b*) estimated an annual incidence of under two in a population of 3,000,000 in Iraq, and none at all in 15 years in British troops. It is surprising, therefore, to find an incidence of the order of one in 4,000 amongst British troops in each of two successive years in one small area of India. Corkhill (1932*b*) found that all the cases of *Echis carinata* bite in Iraq came from one locality and quoted Wall (1913) who stated that *Echis carinata* 'is distributed chiefly in isolated patches where it is frequently very common'.

This is probably the explanation here, for all the British cases and some, at least, of the Indian ones occurred within a mile or two of each other

The first case illustrates the fully developed picture of poisoning by *Echis* venom and will be considered in some detail in the discussion of pathology and treatment. The second case, by contrast, was clinically a successfully treated case, that is, a case where early treatment apparently neutralized completely the local and general actions of any injected venom. The thrombocytopenia and diminished liver function in the second patient are therefore all the more noteworthy. Besides showing that subclinical poisoning may produce quite marked pathological effects, these findings demonstrate that venom was in fact absorbed. Nevertheless, the expected haemorrhagic phenomena did not supervene, which implies that the serum with which the patient was treated, the Haffkine lyophilically dried polyvalent anti-venin, is, in fact, able to neutralize *Echis* venom in man. All anti-venins must be assayed in animals, and it seems important to record this example of success in man.

Numerous *in vitro* activities of *Echis* venom have been described and variously attributed to thrombin, an anticoagulant, lecithinase, proteinase, and haemolysin. There was no trace of haemolysis in the samples of the patient's serum and no anticoagulant activity was demonstrated. The more dramatic actions of the venom in the human subject are local tissue damage and generalized haemorrhage, and these have no obvious counterpart in the factors found *in vitro*. The subsequent analysis of the observations made in these two cases of *Echis* poisoning suggests that the venom has a marked effect on the function of the liver and probably on capillary function also, as illustrated by the haemorrhages and the thrombocytopenia. The apparent involvement of the central nervous system may have been entirely the consequence of capillary haemorrhage. It is becoming increasingly clear that the clinical effects of toxins, including venoms, are often demonstrably due to the enzymatic activity of the toxin itself or to its interference with the activity of essential enzyme systems. In this light the selective action of *Echis* venom on liver and capillaries may be of general interest and significance.

Little is known of the detoxication or excretion of the venom. In the first case bleeding into the urine continued for two days after the bleeding from other sites had stopped, and there was an increasing blood-loss in the urine as the circulation improved. In Robertson's (1935) case, too, the urinary haemorrhage was the last to stop. These facts suggest that *Echis* venom is excreted by the kidneys. Fraser and Gunn (1912), however, in experiments on various mammals, found species differences in the viscera affected by haemorrhage, but that the bleeding into the alimentary canal was the most constant and important. From this they concluded that the venom was probably excreted through the intestinal mucosa, but Taylor and Mallick (1935*b*) found in monkeys that intestinal haemorrhages were inconstant.

The local lesion. The extreme oedema of the bitten limb can be due only

to an obstructed venous circulation. There may be an initial inflammatory oedema which partly obstructs the circulation, but actual venous thrombosis seems necessary to explain the intensity of the oedema and the absence of any detectable circulation. Some small superficial veins were actually seen and felt to be thrombotic in the first case. The cause is probably a combination of slowed circulation, the thrombin effect of the venom, and the tissue damage it causes. The local oedema and extravasation of blood decreased the circulating blood-volume. The dimensions of both legs were measured on the fourth day, and calculation showed that the volume of the affected limb was approximately 2.5 litres greater than the normal leg. What proportion of this was due to extravasated blood it is not possible to determine, but it seemed unlikely to be less than half. The patient retained little fluid during the first 48 hours, so that by then he was certainly dehydrated and oligæmic. This is supported by the immediate improvement in pulse-rate and general condition with a simultaneous fall of 26 per cent in the haemoglobin level resulting from the administration of two pints of blood intravenously and a litre of fluid by mouth. The extent of the patient's fluid need is also shown by the positive fluid balance (in an air-conditioned room) of 4.5 litres during the third and fourth days taken together. After the initial improvement which followed the relief of oligæmia, there was a period of two days when the circulation through the affected limb was restored and the patient's general condition deteriorated. The simultaneous increase in haemorrhage, a specific result of venom-poisoning, suggested that more venom was getting into the systemic circulation. This venom was presumably at first fixed in the leg by its obstructed circulation, and subsequently released as the circulation improved.

The haemorrhagic phenomena. It seems certain in the first case that the blood was initially almost incoagulable owing to lack of fibrinogen, and this confirms the experimental findings of Taylor, Mallick, and Ahuja (1935). The normal clotting time on the third day excludes any gross prothrombin deficiency, and anticoagulant activity could not be demonstrated in the serum. Thus there cannot have been insufficient thrombin for the conversion of the plasma-fibrinogen into fibrin. No fibrinolysin was detectable, and thus it seems that the lack of fibrinogen must have been the result of a failure of production. The source of the plasma-fibrinogen is the liver and the extensive damage to the liver sufficiently accounts for the lack of fibrinogen. There occurred also a not inconsiderable consumption of fibrinogen, for transfusion of nearly five litres of blood of normal fibrinogen-content failed to raise the patient's plasma-fibrinogen to more than a quarter of the normal level. There is no obvious cause for the thrombocytopenia which was found in both cases. In neither case was there a prolonged depression of platelet production, for once the platelet count began to rise, the increase in each case was at about the normal rate of platelet production, 60,000 to 90,000 per c mm. per diem (Toenants, 1938). Bone-marrow activity did not seem depressed in the severer case because large numbers of immature granulocytes were produced. The

most plausible hypothesis seems to be that the platelets were produced in normal numbers, but were consumed in some way directly or indirectly by the action of the venom. This hypothesis would also account for the way the platelet count in the first case overshot the normal level, and then came down to normal later (Fig. 2). An incoagulable blood, complete fibrinogenopenia, and a very severe thrombocytopenia do not by themselves cause haemorrhage (Macfarlane, 1941). The haemorrhage is clearly a specific effect of the venom, but whether this is a direct capillary action or whether indirectly through the liver, it is impossible to say. The former seems more likely since small amounts of Echis venom injected subcutaneously produce local haemorrhagic lesions (Taylor and Malik, 1935*a*). The amount of blood lost by the first patient was very large. The equivalent of 4.84 litres of undiluted whole blood was transfused, after which the haemoglobin level was only 75 per cent. The total blood-loss must, therefore, have been of the order of 6 litres. Of this, 1.5 litres is accounted for by the measured loss in the urine, and probably another 1.5 litres by extravasated blood in the bitten leg, leaving approximately 3 litres for loss by external haemorrhage from skin and mucous membranes and into other tissues. There was no direct evidence of haemorrhage into any part of the body except the skin. Haemorrhage into the brain may have been responsible for the clinical picture during the fifth day and night.

Kidney function. In the first case, once fluids were forced, the urine output was satisfactory. The centrifuged deposit of the urine was free from red cells from the tenth day onwards and there was no urinary albumin after the twelfth day. No casts were seen at any time. Clinical or other evidence of gross renal damage was lacking, although full renal function tests were not carried out. The blood-urea was slightly raised on the sixth day, but fell to normal a few days later. Haemorrhage and the katabolism of extravasated blood are probably a sufficient explanation of the slightly raised blood-urea level. Only isolated observations were made on the urinary 'ammonia'. The remarkable ammoniacal smell of the first specimens of urine and faeces to be passed was initially ascribed to the bacterial decomposition of stale specimens, but the same odour was noted in subsequent fresh samples of urine. The smell was noticeable from about the third to the seventh day. During this time the reaction of the urine was approximately neutral, a finding probably due to alkalis given concurrently with the transfusion and to the buffering effect of the blood it contained. Had the urinary ammonia been due simply to the ketosis of fever and starvation, the urine would almost certainly have been acid in reaction. Furthermore, the ammonia excreted on the fifth day was of the order of 7.5 gm, which is a large amount even for the severest acidosis, and thus some other explanation for the increased excretion is probable. Kellaway (1942) recorded that amines were liberated by isolated organs when snake-venoms were added to the perfusate, and this may provide an explanation for the smell of the urine and for the exceptional output of 'ammonia' as measured by formol titration. These isolated observations in the more severely affected case are recorded as of interest and indicate the

need for further work. In the second case no urinary abnormalities were detected and there was no significant increased excretion of ammonia.

Liver function In the first case the icteric index was raised during the first fortnight (Table I). This may well have been due to a combination of increased haemoglobin destruction in the leg and decreased hepatic excretion. There was a striking, if temporary, increase in urobilinogen excretion in the second case, which may also have been the result of liver damage. The basis of the benzoate detoxication test is not yet fully established, and disturbances of renal function and other unknown factors complicate its interpretation (Sherlock, 1946). With these reservations it can be said that both our cases by this test showed prolonged impaired hepatic function (Table II), a finding confirmed in the first case by the low level of plasma-fibrinogen. The evidence suggests that one of the main toxic effects of *Echis* venom in man is on the liver. The venom indeed appears to have a particularly selective action on the detoxicating function of the liver. Thus, in the first case, while there was a demonstrable failure to produce fibrinogen and excrete bile pigment, both these functions had returned to normal before any benzoate detoxication tests were carried out. In the second case also, though the plasma-proteins and bile excretion were normal, there was impaired ability of the liver to detoxicate as measured by this test. There was in addition a striking correlation in both cases between the slow convalescence and the slow improvement in liver function. Accounts of snake-bite in the standard text-books of tropical medicine for the most part ignore the late results, a slow convalescence, as found in our cases, is not mentioned, but we know at second hand of two other probable examples after viperine-bites. An Indian shop-keeper on the island of Jiwani off the coast of Baluchistan who was also bitten by an *Echis* had not recovered some weeks later, while a British pathologist in West Africa who was bitten on the finger by a Russell's viper in his laboratory, where appropriate treatment was immediately available, did not consider himself normally recovered until 12 months later. Schizophrenia, in contrast to other psychoses, is remarkable for the frequency with which an impaired liver function is found using the benzoate detoxication test (Discussion, 1944). It may be coincidence that in the first patient such an impaired liver function should have occurred before schizophrenic symptoms became manifest, unless the nine hours' delay in reporting sick after being bitten by a snake is considered evidence of pre-existing abnormality. The patient's family history was a poor one, and he may possibly have been predisposed to a toxic psychosis after any severe metabolic disorder.

Treatment The prompt administration of specific anti-venin is agreed to be the most important measure in the treatment of snake-bite. When hours have elapsed since the bite, anti-venin is often considered of doubtful value and local surgical interference then is also condemned as likely to inflict further injury without doing any good. Death after a colubrine-bite occurs within a few hours, due to the neurotoxin fixed in the central nervous system. After a viperine-bite, death takes longer and is not known to be due to such an

irreversible lesion. Death is said to occur between the second and fifth day from haemorrhage, or later from the effects of infection in the bitten part. Time is therefore available for the application of other therapeutic measures. If the pathological deductions in the present paper are correct, the measures to be taken in the management of cases of viperine-bites, after specific anti-venom has been given, are as follows:

1 The bitten part should be elevated and cooled as far as possible to reduce the circulation through it, and hence to retard the absorption of venom. This will also reduce local tissue metabolism so that as little damage as possible will result from the reduced circulation and locally freed venom.

2 Continued blood-transfusion is necessary to maintain the blood-volume and haemoglobin, despite loss of fluid and blood. Fresh blood is preferable to refrigerated blood because its coagulatory and haemostatic properties are probably superior.

3 A very high urinary output should be induced by forcing fluids by mouth and intravenously. It is hoped in this way to accelerate excretion of venom or the toxic products of venom action, and to dilute these toxins and the blood in their passage into the urine, and hence to minimize damage to the kidneys.

We agree with Taylor and Mallick (1935*b*) that no haemostatic or coagulant drugs are of any use, as none of them can overcome the lack of fibrinogen.

Summary

1 Two cases of snake-poisoning by *Echis carinata* are described. The first case was a typical and severe one with a marked local lesion, generalized haemorrhages, and fibrinogenopenia. The second was treated early and showed no such changes. In both cases there was a severe thrombocytopenia, and persistent impairment of hippuric acid synthesis.

2 The pathology of *Echis*-poisoning is discussed in the light of the investigations made, and it is suggested that in man the main sites of action of the venom are the liver and the capillaries.

Our thanks are due to the Director-General of Medical Services, Royal Air Force, for permission to publish this paper.

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THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1947

FORTY-FIRST ANNUAL GENERAL MEETING

THE FORTY-FIRST ANNUAL GENERAL MEETING was held in Aberdeen on Friday and Saturday, May 23 and 24, in the Medical School at Foresterhill. The attendance book was signed by 106 members. The proceedings began at 10 a.m.

The President, Professor A. W. M. Ellis, was in the Chair.

Deaths of Honorary Members The President reported with regret the deaths of Professor T. Wardrop Griffith, referring to his eminence in the profession and his presidency of the Association at Leeds in 1934, and of Sir F. Gowland Hopkins, in whom the Association has lost one of the greatest of biological chemists.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read, confirmed, and signed.

The Treasurer presented the Annual Accounts, which showed a balance of £581 8s 1d. In addition to this the Association held £360 in the Post Office Savings Bank, and £2,000 in investments. The financial position was very satisfactory and the Executive Committee had recommended that a further £300 be deposited in the Post Office Savings Bank. The accounts and the above recommendation were accepted by the Association.

Selection of Place of Meeting for 1948 The Secretary read letters from Dr. Perry Pepper, President, and Dr. Wearns, Secretary, of the Association of American Physicians, regretting the impossibility of a joint meeting of the two Associations this year in America, and expressing the hope that it might be possible to hold the joint meeting next year, and a personal letter from Professor W. S. Middleton to the same effect. It was agreed that it was impossible at the present moment to say whether transport and currency difficulties would permit of a joint meeting in 1948, and that, in any case, there should be an Annual General Meeting in Great Britain. Invitations had been received from Liverpool, Belfast, and Dublin, and it was agreed provisionally that the Association should meet in Liverpool in 1948, in Belfast in 1949, and in London in 1950.

Number of Extra-Ordinary Members in 1948 In view of the large number of candidates for Ordinary Membership, the Association agreed to leave to the discretion of the Executive Committee the nomination of up to 15 Extra-Ordinary Members in 1948, to provide as many places for new members as were deemed desirable.

Election of Officers

President Dr. A. Greig Anderson was elected President. On his election he took the Chair, and expressed the thanks of the Association to the retiring President, Professor A. W. M. Ellis.

Election of Officers, Executive Committee, Honorary Members, Extra-Ordinary Members, and Ordinary Members then followed.

Executive Committee

President Dr. A. Greig Anderson

Treasurer Professor L. J. Wills

Secretary Dr. C. E. Newman

Members for England

Sir Adolphe Abrahams
 Dr D Evan Bedford
 Dr E Bulmer
 Sir Charles Symonds
 Dr Robert Coope
 Professor C H Stuart-Harris

Members for Scotland

Dr J N Cruickshank
 Dr A Rao Gilchrist
 Dr T N Morgan

Members for Ireland

Dr R S Allison
 Dr T H Crozier
 Dr D M Mitchell

Election of Honorary Member

Professor A W M Ellis (President 1946-7)

Election of Extra Ordinary Members

Sir Adolphe Abrahams
 Dr A E Barnes
 Professor J C Bramwell
 Dr S B B Campbell
 Dr R C Clarke
 Dr Foster Contes
 Dr R Coope
 Professor Sir Francis Fraser
 Dr A Hope Gosso
 Dr W Johnson
 Dr J Parkinson
 Dr D Paterson
 Dr S W Patterson
 Dr J M Smellie
 Professor W. W D Thomson

Election of Ordinary Members

Douglas Andrew Kilgour Black, M D, Lecturer in Medicine, Manchester University
 Archibald Malcolm Gordon Campbell, D M, Honorary Physician, Bristol Royal Hospital
 John Halliday Croom, F R C P E, Assistant Physician, Royal Infirmary, Edinburgh
 David Howard Davies, M R C P, Honorary Physician, Bristol Royal Hospital
 Oliver Fitzgerald, M D, Senior Assistant Physician, St Vincent's Hospital, Dublin
 Charles Montague Fletcher, M D, Director, Medical Research Council Pneumococcosis Research Unit, Cardiff
 Ian Gordon, O B E, F R C P, Assistant Physician, Aberdeen Royal Infirmary
 Graham William Hayward, F R C P, Assistant Physician, St Bartholomew's Hospital, London
 Leonard Hayden Howells, M D, Physician, Cardiff Royal Infirmary
 Martin Hynes, M D, Reader in Medicine, University of Cambridge
 Alexander Henderson Imrie, F R F P S, Assistant Physician, Royal Infirmary, Glasgow
 Arthur Morgan Jones, M R C P, Rockefeller Fellow of the Medical Research Council
 Alan Kekwick, F R C P, Assistant Physician, Middlesex Hospital, London
 John Duke Olav Kerr, F R F P S, Dispensary Physician, Western Infirmary, Glasgow
 Austin William Drevar Leishman, D M, Honorary Physician, Royal Infirmary, Sheffield
 Henry George Miller, M D, Assistant Physician, Royal Victoria Infirmary, Newcastle-on-Tyne
 Denis Kenry O'Donovan, M D, Visiting Physician, St Vincent's Hospital, Dublin
 Kenneth Murray Allan Perry, M D, Assistant Physician, The London Hospital

Edward Eric Pochin, F R C P, Physician, University College Hospital, London
 Richard Wainwright Duke Turner, O B E, M D, Senior Lecturer, Department of
 Medicine, University of Edinburgh

SCIENTIFIC BUSINESS

Friday Morning May 23

I DR JOHN F WILKINSON described the results of *Folic Acid in the Treatment of Anaemia*. In general folic acid or its conjugates were of no value in the treatment of aplastic or hypoplastic anaemias, agranulocytosis and leukopenias from various causes, hypochromic anaemias, most refractory macrocytic anaemias (usually with normoblastic marrows), all types of leukaemias, leuco erythroblastic anaemia, chronic ulcerative colitis, anaemias secondary to myxoedema or hypothyroidism, or the purpuras. On the other hand, folic acid had good haematological and clinical effects on macrocytic anaemias with megaloblastic marrows, such as pernicious anaemia, the macrocytic megaloblastic anaemias of pregnancy, infancy, pellagra, sprue, steatorrhoea, and coeliac disease, nutritional macrocytic anaemia, and possibly achrestic anaemia. It acted equally well when given orally or parenterally and had no ill effects, the usual dosage being 15 to 20 mg daily orally. In pernicious anaemia the haematological responses were similar to those seen with liver preparations, but after 12 months a number of patients tended to relapse and required increasing doses of folic acid. On the other hand, folic acid was unable, in very large doses, to relieve or prevent the onset and progression of subacute combined degeneration of the cord, in fact there was a very disconcerting tendency for subacute combined degeneration of the cord to develop quickly. Folic acid was therefore contra-indicated, and was neither as efficient nor as cheap as liver or stomach extracts in the treatment of pernicious anaemia. In sprue, coeliac disease, and idiopathic steatorrhoea, the responses were variable, the megaloblastic anaemias often showing good responses at least for a time.

PROFESSOR WITTS commented on the tendency to regard milk as a poison because babies became anaemic on a milk diet. He pointed out that they were not necessarily anaemic at all, we might be judging by a wrong standard. Sprue was actually treated with milk, which contains large amounts of folic acid. The action of folic acid appeared to be to dry up the stools rather than to diminish their fat content. This relieved the patient of dehydration and so improved his general condition.

DR C C UNGLEY had had experience of sprue in pregnancy. The macrocytic anaemia improved with folic acid, but the stools increased in looseness and frequency. This might have been associated with worry, but folic acid did not always dry up the stools. He pointed out that since doses of liver extract, which are effective in the treatment of anaemia, may have no effect on the spinal cord, so folic acid might be effective if given in larger amounts.

DR F PARKES WEBER asked whether anyone had tried the effect on the spinal cord of folic acid combined with intensive iron treatment. The effect of iron on pernicious anaemia had been found to be great in the days before modern therapy, but this fact seemed to have been forgotten.

PROFESSOR L J DAVIS said that in a series of cases of sprue treated with folic acid it had been found that in none was there any improvement in the absorption of fat, but that all improved subjectively and in the radiological appearance of the small intestine. He had found that in the treatment of subacute combined degeneration of the cord intensive treatment with liver was unnecessary, enough to control the anaemia prevented degeneration of the spinal cord.

DR WILKINSON replied that although milk contains folic acid it is possible to produce anaemia in rats on a diet of milk. The amount of folic acid in liver extract is minute. Subacute combined degeneration does not respond to doses of 80 to 100 mg of folic acid. He had not tried the effect of folic acid combined with iron, but he deplored the appearance on the market of 'blunderbuss' mixtures of folic acid, iron, copper, etc., the therapeutic contents of which were wholly inadequate. He pointed out the difficulty of assessing the effect of treatment on sprue, a disease which is essentially phasic in its natural history. He stressed that sprue in Cuba is entirely different, being a gross nutritional disease.

DR H H MOLL commented on a case of sprue syndrome with megaloblastic anaemia due to tuberculous enteritis, and said that a radiogram of the abdomen showed a large

number of calcified mesenteric glands, the anaemia was refractory to liver therapy, but responded promptly to folic acid. Folic acid produced temporary symptomatic improvement, but did not control the steatorrhoea and also did not prevent a relapse.

2 DR H W FULLERTON described a *Case of Cyclical Agranulocytosis* in a man of 64 years. Since the patient first came under observation in June 1946 he had had regular attacks in which the neutrophil polymorphs disappeared completely from the blood. The intervals between the attacks varied from 25 to 28 days, and in each attack there were pyrexia and infections, especially in the mouth and throat. Examinations of the sternal marrow made at intervals throughout one cycle showed that the phases of agranulocytosis were due to a virtual disappearance from the marrow of the precursors of neutrophil polymorphs. Various forms of treatment, including pent-nucleotide injections, benadryl, Lertigon injections, and pyridoxine, failed to modify the course of the illness. Splenectomy was performed in March 1947. Since then the cyclical variation in the number of neutrophil polymorphs had continued, but complete absence of these cells had not occurred and the patient had not suffered from further bouts of pyrexia and infections.

3 PROFESSOR L J WITTS spoke on *Splenectomy in Chronic Neutropenia*. While penicillin had revolutionized the treatment of acute agranulocytosis there remained a small number of patients with persistent leucopenia in whom a lasting elevation of the white cell count was desirable. Leucopenia usually precluded treatment by X-radiation or radio active materials, nitrogen mustard, and urethane. The white count usually rose and remained high after removal of the spleen, whether the spleen was normal or pathological. On this account the spleen had been removed in cases of sarcoidosis, Hodgkin's disease, and lymphoid follicular reticulosis, and the results had been satisfactory. Cases of chronic agranulocytosis of a primary or idiopathic type probably fell into two classes, one a variant of aplastic anaemia, the other a variant of haemolytic anaemia. Examples of each of these classes were reported in which splenectomy had not relieved the symptoms, though the work of Doan and others showed that splenectomy was sometimes successful in the haemolytic type of leucopenia.

DR F PARKES WEBER recalled a case seen at the Royal Society of Medicine of cyclical agranulocytosis combined with a cyclical psychical syndrome. He commented on possible relationships with rheumatoid arthritis, the most mysterious of all diseases, and stressed the need for research work on rheumatoid arthritis.

PROFESSOR L J WITTS asked if DR FULLERTON had attempted to transmit the disease from his case to animals. DR FULLERTON replied that he had not. He had transfused the plasma from a pint of the patient's blood into a human recipient to see if there was any factor present in the serum, but without effect.

4 DR A R KELSALL, MR G HIGGINS, and MR J R P O'BRIEN (introduced) with DR ALICE STEWART and PROFESSOR L J WITTS gave a communication on *Ascites in Subacute and Chronic Hepatitis*. DR KELSALL said that among 35 cases of subacute and chronic hepatitis ascites occurred in 19, none of the patients were chronic alcoholics. In seven ascites was continuous, while in 12 it was temporary or intermittent. The prognosis after the appearance of ascites is not as bad as is often stated. There was a correlation between the occurrence of ascites and of increased portal pressure, as judged by the presence of splenic enlargement and oesophageal varices. Portal vein thrombosis and chronic peritonitis were each found once only. A study was made of the relationship between ascites and plasma colloid osmotic pressure (COP), calculated from 193 estimations of the plasma protein levels. It was found that ascites seldom occurred unless the plasma COP was below normal, very low levels of plasma COP, however, did not always lead to ascites, even in the presence of marked portal hypertension. Moreover, in individual patients, although the plasma COP was usually lower when ascites was present than when it was absent, this was not invariable. Pleural effusions occurred in 10 patients, there was no evidence of tuberculosis in these cases and the plasma COP was below normal in all of them.

DR B SCHLESINGER asked why, if the low plasma osmotic pressure was the cause of ascites, these patients would not develop oedema elsewhere.

PROFESSOR R PLATT commented that it was very odd that there were so many non-alcoholics in PROFESSOR WITTS's series. He was suspicious of histories based on past records and felt that it was essential that inquiry about alcoholic causes should be undertaken personally.

PROFESSOR J W MCNEE had noted that female patients with infective hepatitis progressing to cirrhosis greatly outnumbered male patients. He suspected that there might be a good deal of non-alcoholic cirrhosis in the future, and thought that, as a result of all the cases of infective hepatitis during the war, there might be a good deal of chronic hepatitis in this country at the moment. He was very concerned over the great difficulty of the pension problem in cases of patients with possible chronic hepatitis who had not been jaundiced in the acute attack.

PROFESSOR WITTS replied that he was quite happy about the histories in his series, it would need a clever patient to conceal alcoholism from DR ALICE STEWART. The population from which the series was drawn was rural or semi-urban, in which the incidence of alcoholism was low, and they were most of them respectable married women. He thought that the good results of treatment claimed by the Americans could be explained by the fact that their cases were for the most part alcoholic and dietetic. The results in Oxford had been disappointing, probably because the pathology was different.

PROFESSOR CLIFFORD WILSON had seen patients with a normal amount of plasma protein, but with signs of increased portal pressure, who had no ascites or oedema. He suggested that as the quantity of posterior pituitary hormone in the urine was increased in cirrhosis with ascites, and as the post-infective cases often had angiomas, which are associated with oestrogen metabolism, he thought it possible that ascites might be associated with abnormal endocrine metabolism.

THE PRESIDENT inquired how one was to know if patients who had had infective hepatitis were left with impairment of hepatic function. He also was anxious with regard to the problem of pensions.

DR KELSALL, replying, said that he would not for a moment suggest that the plasma osmotic pressure was the only factor concerned, but that, as a matter of fact, many patients with ascites do have oedema elsewhere. He pointed out that in a recent paper in the *Quarterly Journal of Medicine* on hunger oedema, it had been found that it was not just a question of an oedema level of plasma protein, low protein osmotic pressure was one factor, increase in portal pressure was probably another. He also was quite satisfied that the incidence of non-alcoholic hepatitis had not been over estimated, and he felt that the responsibility of infective hepatitis for the subsequent cirrhosis was very important to the patient. He agreed that the problem about pensions was very difficult. In answer to the PRESIDENT's question he pointed out that although in a single test the liver function may be normal in a case of cirrhosis, multiple tests will reveal some abnormality, just as clinically any one physical sign may be absent, whereas most patients have some physical sign of the disease.

5 DR W A PARKER (introduced by PROFESSOR NOAH MORRIS) described the *Clinical Pharmacology of Sodium Salicylate*. Plasma levels of salicylate were estimated in patients after various methods of administration of sodium salicylate. After single doses the peak plasma level appeared in two hours. Little difference was detected between two hourly and four-hourly administration. The administration of alkali led to a fall in salicylate plasma levels, while administration of an acid salt produced an increase. These results were probably due to an increased rate of excretion with alkali and a decreased rate with acid. There is an increase in the ratio 'free salicylate in the urine/total salicylate administered', with increased alkalinity of the urine. By means of rectal administration it was possible to maintain plasma levels of the same order as with oral administration. With intravenous administration higher levels could be obtained, but only for a short period, so that with oral therapy it is possible to maintain as high a constant level. It was possible to prevent reduction in alkali reserve of the blood with simultaneous intravenous administration of sodium lactate solution. The incidence of toxic manifestation was described and was related to plasma levels. From the figures obtained it was suggested that vomiting is caused by a central effect in rectal and intravenous administration and by a local effect in oral administration.

DR F PARKES WEBER pointed out that acute rheumatic fever was a series of phenomena due to hypersensitivity towards the unknown pathogenic agent of rheumatic fever. If this agent is a streptococcus or virus, salicylates act on the hypersensitivity and not on the pathogenic organism. He commented that the very severe forms of rheumatic fever which used to be seen seemed to have diminished with the improvement in the general nutrition of young people.

1 p m

The Association then adjourned to luncheon at the University. After luncheon parties were shown over the new Infirmary buildings, and pathological and pharmacological demonstrations were exhibited in the Medical School.

3 30 p m

The Association was entertained to tea by the Directors of the Infirmary in the new Nurses' Home.

4 p m Afternoon Session

1 DR C G BARNES described two patients with *Benign Cavernous Haemangioma of the Lung*. The tumours acted as arteriovenous aneurysms in the pulmonary circuit causing cyanosis, clubbing of the fingers, polycythaemia, haemoptysis, and attacks of cerebral anoxaemia, there was no cardiac enlargement. Slides were shown illustrating the typical X ray appearances and structure of the haemangiomas, and the value of tomography in the diagnosis of these cases was stressed. Dr BARNES emphasized the differential diagnosis from congenital heart disease in children and from polycythaemia rubra vera in adults. Lobectomy was performed on each patient, although the first died from post-operative pneumonia the second did well and would probably be completely cured.

DR PARKES WEBER said that Dr BARNES had illustrated one form of the dysplasia of the blood vascular system and had thrown an interesting additional light on vascular hamartomata.

2 DR A RAF GILCHRIST spoke on *Infective Endarteritis of the Pulmonary Artery*. In a series of 60 consecutive cases of patent ductus arteriosus observed during the past six years, infective endarteritis of the pulmonary artery had developed in six patients. The local lesion was similar in its aetiology, pathology, and course to the better-known subacute bacterial endocarditis. The diagnostic triad consisted of septicaemia, local signs of a patent ductus, and recurrent pulmonary infarcts, but it was desirable to establish the diagnosis before embolic phenomena occurred. In successful treatment surgical closure of the ductus was of outstanding importance and took precedence of chemotherapy, though penicillin could be used in the more gravely ill patient, judged too exhausted for immediate surgical intervention, in a dose of 500,000 units daily for 28 days, in the hope of overcoming the infection and thus preparing the way for ductal ligation. The risks of pulmonary infarcts during the first few weeks of penicillin therapy were very real and might well offset any gain in the patient's strength and resistance. Three patients in the series of six recovered, two of whom were treated exclusively by surgery and one with penicillin preparatory to ligation. The most effective step in the prevention of infective endarteritis is the recommendation that all children known to have a patent ductus should be kept under observation until the age of seven or 10 years, about which time ligation should be performed. The development of a *Streptococcus viridans* septicaemia could be prevented by the use of intensive sulphonamide therapy before and during operations on the mouth and throat. In this way the incidence of bacterial endocarditis and infective endarteritis should be reduced.

PROFESSOR J C SPENCE pointed out that these patients might not be improved by penicillin and that operation while the patient was still in a deplorable clinical state might succeed with the help of great pre operative and post-operative care.

PROFESSOR J C BRAMWELL advocated prophylactic treatment before dental treatment in all cases liable to septic endocarditis. He thought that patients who had been infected for any length of time with endocarditis had not responded to treatment as well as had recent infections of, say, under 10 weeks.

DR GILCHRIST agreed that it was unwise to postpone surgery too long and thought that it was wiser to take risks with children even if it was not with adults. In his opinion a very exhausted adult patient with a protracted infection should be treated with penicillin before operation.

3 PROFESSOR CLIFFORD WILSON discussed the *Relation of Hypertension to the Development of Renal Failure in Chronic Bright's Disease*. During the course of chronic nephritis impairment of renal function was frequently preceded by a rise in blood-pressure, which particularly affected the diastolic level. This rise was in most cases

gradual and was not associated with signs of reactivation of the nephritis. The rate of deterioration of renal function was related to the subsequent behaviour of the blood pressure. In some cases the diastolic pressure rose rapidly and became fixed at a high level in a period of months. Papilloedema, left ventricular failure, and hypertensive encephalopathy developed, and although renal impairment was rapidly progressive the patient died with only moderate nitrogen retention, in fact the clinical picture was indistinguishable from that of malignant hypertension. When this syndrome occurred in primary renal disease he suggested that the term malignant termination should be used to avoid confusion with the malignant form of essential hypertension. Other cases of chronic nephritis developed renal failure more slowly. In these the diastolic pressure tended to be only moderately raised and was labile, but the majority of cases ended with a malignant termination. Of a series of 127 cases of uraemia in which histological examination of the kidneys was made, 49 were diagnosed as malignant hypertension and 57 as chronic nephritis, 61 per cent of the latter developed the malignant termination described above.

PROFESSOR ELLIS stressed the differentiation between malignant hypertension and renal disease associated with a hypertensive termination. Malignant hypertension was primarily a vascular disease, the others were primarily renal.

PROFESSOR PLATT, discussing the difference between malignant hypertension and cases of renal, if of obscure renal, origin, pointed out that, contrary to what was thought, the secondary cases were usually young, but that the cases of primary malignant hypertension were rather older, the average age being about 47 years.

DR GILCHRIST thought that uraemia was sometimes postponed by cardiac failure, as for instance that after coronary thrombosis.

PROFESSOR CLIFFORD WILSON thought that the rise in blood pressure was due to renal ischaemia. He pointed out that renal function certainly does not improve with cardiac failure, though the fall of blood-pressure may in some cases postpone renal failure.

4 PROFESSOR ROBERT PLATT discussed *Heredity in Hypertension*. Because hypertension is a syndrome and not a disease any study of heredity must clearly distinguish essential hypertension from hypertension secondary to other causes, such as pyelonephritis and urological disorders. Failure to do this is the chief reason why the overwhelming influence of heredity in essential hypertension has not been fully appreciated in the past. When the distinction between essential and secondary hypertension was carefully made it was found that the family histories in secondary hypertension resembled those of a control group with normal blood pressure, whereas in essential hypertension the frequency of a positive parental history strongly suggested the action of a dominant gene with a rate of expression of over 90 per cent. This was important in practice. For instance, if there was strong evidence that a parent had had hypertension there was a 5 to 1 chance that the patient's hypertension was of the essential type. If there was evidence that the parents were unaffected the chances were 5 to 1 against essential hypertension. The hereditary factor in the malignant and benign types of essential hypertension appeared to be the same.

THE PRESIDENT said that doctors working in not too big a town could follow the family histories of their patients and were aware of the hereditary factor in hypertension.

PROFESSOR CLIFFORD WILSON thought that family history might be very useful in differentiating primary from secondary hypertension, and noted that recent American work had confirmed PROFESSOR PLATT'S findings.

PROFESSOR ELLIS was surprised that PROFESSOR PLATT had been able to obtain such satisfactory evidence. He asked whether PROFESSOR PLATT had considered his cases in the light of the Registrar General's classification of the four economic classes. PROFESSOR PLATT said that he had not investigated his cases from the economic point of view, but that he had no doubt that such an investigation would be interesting. He remarked, however, that as he had just taken on a whole time appointment he was afraid his monograph on the diseases of the very rich would never be written.

Annual Dinner

The Annual Dinner was held in the Elphinstone Hall of King's College, Aberdeen. The President, DR A. GUNN ANDERSON, was in the Chair. The toast of the Association was proposed by the President and that of the Guests by PROFESSOR D. M. DUNLOP.

The Principal, SIR WILLIAM HAMILTON FYFE, replied, and SIR THOMAS MITCHELL, the Lord Provost of Aberdeen, added a few remarks on behalf of the city. The toast of the President was proposed by DR GEORGE RIDDOCK. The other official guests were MR A BURNETT WRIGHT, Chairman of Directors, Royal Infirmary, PROFESSOR J S YOUNG, Department of Pathology, Aberdeen University, and DR A W HENDRY, Senior Physician, Aberdeen Royal Infirmary. There were present 109 members and guests, and in the opinion of all both the dinner and the speeches were of an outstandingly high quality.

Saturday, 10 a.m. Morning Session

1 DR A M G CAMPBELL (introduced by DR W RITCHIE RUSSELL) discussed *The Association between Swayback and Disseminated Sclerosis*. He reported that four of seven research workers studying 'swayback' in sheep developed a disease of the central nervous system resembling disseminated sclerosis. Both swayback and disseminated sclerosis are demyelinating diseases, and both have a geographical distribution. Swayback is prevented by giving copper salts to the ewes, but the treatment of disseminated sclerosis with copper salts had so far proved to be disappointing.

THE PRESIDENT said that disseminated sclerosis was common in Aberdeen and reminded the Association that DR D ADAMS of Glasgow had read a paper on disseminated sclerosis in wood workers.

DR D MCALPINF suggested that disseminated sclerosis was at least as mysterious as rheumatoid arthritis. The difficulty was that it seemed likely that the cause was not in the nervous system but outside it. The problem, therefore, lay in the scope of the physician, not in that of the neurologist. It might be either a specific allergic response or a specific infection. There was a small but definite familial incidence and there were many obscure factors determining the onset, such as trauma or psychological events.

DR RITCHIE RUSSELL said that the relationship of copper to disseminated sclerosis had been investigated, but that copper metabolism had been found to be within normal limits. Workers on swayback in 1939 who were afraid that they might be being infected had, as a matter of fact, used copper on themselves. The progress of the disease in infected workers had been benign with one exception, in which treatment with copper sulphate had not prevented relapses, and the patient had possibly run the risk of copper sulphate cirrhosis. The theory that a virus infection might be influenced by trace elements opened fascinating possibilities.

DR ALLISON said that he had investigated disseminated sclerosis in wood-workers. He had found no evidence of geographical distribution, and no evidence that it was more prevalent in urban or rural districts. It had been impossible to decide when the disease began in relation to employment because of movements of the population. He suggested the possibility of progress by the measurement of the duration of relapses and remissions.

DR MCCLUSKIE had found that the incidence of disseminated sclerosis was highest in innkeepers, farmers, and wood-workers, in that order. The possibility of an insect vector was being investigated by a study of the insects infesting different animals and woods. He had inoculated sheep from patients with acute disseminated sclerosis with out result, but had not investigated the effect of inoculation combined with deficiency of trace elements. He thought it possible that the Cambridge workers might have been infected by the bites of insects from the bodies of dead animals.

PROFESSOR ELLIS suggested that a latent infection might be responsible for the relapses, and remarked that as a sufferer from herpes febrilis he was all too aware how a latent infection could be lit up by factors of many different kinds.

PROFESSOR OLIVER suggested that as copper is present in all tissues except yolk of egg there might be a relation between infection and a deficiency of eggs in the diet.

DR BURROW pointed out that virus diseases in animals did not necessarily take the same form when they appeared in man. Louping ill appeared in sheep as a cerebellar atrophy, but in man resembled tuberculous meningitis. He instanced cases of female patients who suffered from what appeared to be tuberculous meningitis and recovered, and who were found to have been concerned with louping ill. He noted that in cases of louping ill in man the chlorides in the cerebrospinal fluid were normal. He said that disseminated sclerosis in the Leeds district had a higher incidence in country folk than

in townspeople, particularly in farm workers and gamekeepers. He also suggested the closer study of natural remissions and relapses, and hazarded the suggestion that as the central nervous system is isolated from the blood by reticulo endothelial cells, damage to these cells by circulating antibodies might be responsible. He noted the remarkable results sometimes produced by hyperthermia and arsphenamine.

DR CAMPBELL replying, instanced an outbreak of disseminated sclerosis in a village in which the affected girls had passed through a saw-mill on their way to school and drunk water from a well contaminated with sawdust, but noted that association with wood workers and a familial incidence were only occasionally found. He agreed that inoculation experiments were worth doing, but commented on the expense of the sheep as an experimental animal, and said that the copper content of the liver in disseminated sclerosis had been found to be normal in biopsy material.

2 DR I ANDERSON (introduced by DR J CRAIG) described *Minor Degrees of Adrenal Virilism*. Nine unselected female cases of post-pubertal hirsutism showed few signs of virilism other than masculine hypertrichosis. The urinary 17-ketosteroid output was slightly above the normal range in five cases, who also had 100×17 -ketosteroid creatinine ratio of over unity, and an abnormally high proportion of 3β 17-ketosteroids in the total 17-ketosteroid output. In two cases with raised 17-ketosteroid output, the adrenal glands were of normal size radiologically after perirenal insufflation, and Soffer's salt tolerance test gave normal results. One case showed insulin resistance in the glucose insulin tolerance test. Both patients were given oestrogen therapy. One mg of dienestrol daily for two months tended to regularize menstruation, but had no effect on the hirsuties or the 17-ketosteroid output. Five mg of dienestrol daily for six weeks produced no further change in one case, but in the other there was a decrease in the darkness and coarseness of the facial hair and the 17-ketosteroid output fell to a normal level.

PROFESSOR PLATT commented that he had had two cases in hospital recently and had observed some familial incidence. He stressed that Cushing's syndrome was due to different hormones, and although the Cushing and adrenogenital syndromes might coincide in the same individual, they should be clearly separated in the mind.

3 DR J F PATTERSON (introduced) and DR S ALSTEAD speaking on *The Treatment of Intestinal Flatulence* said that drugs and methods employed to relieve gaseous distension of the bowel were legion. Hitherto assessment of their relative merits had been on general clinical lines, mainly dependent on the subjective sensations of the patient. The method described consisted in measuring the output of gas from the bowel by means of a self-retaining catheter inserted into the rectum and connected with the common gas jar. Controlled observations could thus be attempted, and results showed that the only reliable therapeutic measure was the subcutaneous injection of posterior pituitary extract in full doses. Hot turpentine stupes, radiant heat, carbachol physostigmine, prostigmine, and carminatives proved more or less unsatisfactory.

4 DR D A K BLACK (introduced) discussing *Fat Absorption in Tropical Sprue* said that the serum levels of total fatty acid, cholesterol, and lipid phosphorus were determined before, and at intervals after, a standard meal containing 18 gm of fat. Twelve such curves were done on normal controls, and 31 on patients with early tropical sprue. From these observed values the changes in phospholipide, cholesterol bound, and neutral fat, and fatty acid were calculated. It was found that the fasting values for cholesterol and phospholipide fatty acid were lower in sprue, while neutral fat rose to about the same degree as in normals. The normal range of increment in the various fractions is wide, and fat curves have no diagnostic value in the individual patient. The results are in accord with Stannus's hypothesis that neutral fat is well absorbed in sprue, while the absorption of split fat is impaired.

DR. BLACK, in reply to a question by PROFESSOR PLATT, said that the results of this investigation had not at present altered the treatment of sprue.

5 DR S W PATTERSON described *Some Unusual Complications of Para-oesophageal Hernia*. The development of the condition is interesting from the point of view of surgical anatomy. The symptoms when present are similar in short oesophagus and para oesophageal hernia and are commonly characterized by their intermittency and their relation to posture. There may be no symptoms, when there are they fall into groups (a) Pseudo anginal, pressure pain in the lower chest often referred to the left

shoulder The mechanism of these symptoms may be from local distension or from stimulation of the sensory endings of the vagus or of the phrenic nerves Mathison (*Rev. of Neur and Psych* (1912), 10, 553) found alterations of blood pressure and respiration on stimulating the central end of the cut phrenic nerves in dogs, cats, and rabbits (b) Embarrassment of breathing and pressure in the mediastinum (c) Digestive symptoms such as dysphagia, haematemesis, or ulcer of the affected portion of the stomach An unusual case of leiomyoma of the herniated part of the stomach, with strangulation and haemorrhage, successfully operated on by Mr Hermon Taylor, was described

THE PRESIDENT pointed out that para-oesophageal hernia produced three different clinical pictures, the cardiac, the mediastinitic, and the digestive .

6 DR IVOR DAVIES described the *Clinical Features of Pneumoconiosis* and referred to the recent communications on the Medical Research Council Research in Cardiff by DR ALICE STEWART and DR C M FLITCHER Dust prevention in mines was being energetically pursued and preliminary measures were promising He had first noticed the frequency of emphysema in colliers at the Out-patients Department of the Cardiff Royal Infirmary as far back as 1914, and over 20 years had observed its slow development, when, after 20 to 30 years in the mine, the chest expansion would be reduced to two inches and about 10 years later to one inch or even less Many men working at the coal-face were found to be prematurely old at 50 years through emphysema and sometimes cardiovascular degeneration An offer to investigate was rejected by the Miners' Union through a fear of the economic consequences Advanced emphysema obscured silicosis, tuberculosis, and cardiac enlargement Later, in hospital, he found that right-heart failure was the cause of death in most cases and simple bronchopneumonia in the remainder Most of the cases of silicosis died at home from tuberculosis Several striking specimens of lungs were demonstrated These were sections prepared by Dr Jethro Gough and Mr J E Wentworth in the Department of Pathology of the Welsh National School of Medicine, by embedding a slice of the expanded lung in gelatin and mounting sections about $\frac{1}{4}$ mm thick on paper They were demonstrated by transmitted light on an X-ray viewing-box

PROFESSOR WITTS commented on the beauty of the large microscopic sections, and thought they represented a great advance in the technical methods of investigation

DR PARKES WEBER, commenting on the dust caused in London by the distribution of coal, wondered why the coal distributors do not suffer in the same way as miners

DR YOUNG said he had only seen one coal distributor with anthracosis in 20 years' experience

DR DAVIES said that the Medical Research Council Report of 1942 showed that length of time at work and the concentration of dust were the important factors

I p m

The Association lunched at the University, and PROFESSOR ELLIS proposed a vote of thanks to the local members for their hospitality and for having organized so successful and enjoyable a meeting This was received with acclamation In the afternoon the Chapel, and the books and manuscripts in the Library of King's College were exhibited

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